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Effects of Osteoarthritis and Chronic Pain Management for Companion Animals

Rebecca A. Cason
Southern Illinois University Carbondale, rac89@siu.edu

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EFFECTS OF OSTEOARTHRITIS AND CHRONIC PAIN MANAGEMENT FOR COMPANION ANIMALS

By

Rebecca A. Cason

B.S., Southern Illinois University Carbondale, 2012

A Research Paper

Submitted in Partial Fulfillment of the Requirements for the

Master of Science.

Department of Animal Science, Food and Nutrition

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Approved by:

Rebecca Atkinson, Chair

Amer AbuGhazaleh

Nancy Henry

Graduate School
Southern Illinois University Carbondale
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SYNOVIAL JOINT ANATOMY AND PHYSIOLOGY

Before discussing osteoarthritis (OA) in companion animals, one must understand the synovial joint anatomy and physiology of an animal. The synovial joint is the most common joint and most complex type of joint found in the body. It contains synovial fluid that has three primary functions: lubrication, nutrient distribution, and shock absorption. This fluid is found in the synovial cavity of a joint, which is the space enclosed by the articular capsule. The articular capsule is a fibrous capsule that is continuous with the periosteum of articulating bones. It consists of two layers; the outer fibrous layer and the inner synovial layer. The outer fibrous layer is made up of white fibrous tissue, called the capsular ligament. Its role is to hold together articulating bones and support the synovium. The synovium is the inner synovial layer, a highly vascularized layer of connective tissue. It absorbs and secretes synovial fluid, and is responsible for the mediation of nutrient exchange between circulating blood and the joint. The bones of a synovial joint are covered by a thin layer of hyaline cartilage, which serves to line the epiphysis of the bone. The cartilage provides a smooth surface and has two functions; it minimizes friction upon joint movement and absorbs shock.

Capsular ligaments are another important part of the synovial joint. They are made up of bundles of dense connective tissue that are highly adapted for resisting strain to prevent extreme movements that may damage articulation. Dense connective tissue consists predominately of extracellular matrix (ECM) and the ECM contains a multitude of structural fibers. These structural fibers are made up of crossed linked fibrillar proteins, hydrated gelatinous interfibrillar matrix containing an array of nonfibrillar proteins, proteoglycans (PGs), glycoproteins, proteolipids, and polysaccharides. Furthermore, connective tissue also contains cells called progenitor cells. These cells, represented in small numbers, play an important role in repair,

regeneration, and adaptive modeling of connective tissues. Next, a bursa is a small sac lined by the synovial membrane and filled with synovial fluid. They are placed at key points of friction in a joint, providing the joint with free movement. They can become inflamed following infection or irritation by over-use of the joint. Joints have a rich nerve supply provided by articular nerves. The nerves of a joint transmit impulses which play a key role in proprioception. Furthermore, joints receive blood through articular arteries, which arise from the vessels around the joint. The articular arteries are located within the joint capsule, mostly in the synovial membrane. A common feature of the articular arterial supply is frequent anastomoses by collateral channels in order to ensure blood flow to and across the joint regardless of position of joint. The articular veins accompany the articular arteries and are also found in the synovial membrane.

The molecular components of ECM are collagen, elastin, and proteoglycans. Collagen is the most abundant protein in the body. There are several groups of collagens, but of primary importance are the fibrillar collagens. Fibrillar collagens make up the major structural components of connective tissues such as tendons, ligament, cartilage, and bone. There are three different types labeled; type I, type II, and type III. Type I collagen forms linearly and has extensively crossed-linked macromolecular structures that impart high tensile strength to tendons and ligaments (Zink and Van Dyke, 2013). Type II collagen fibrils with articular cartilage are cross-linked into extensive three-dimensional networks that provide resistance to deformation in a multitude of directions (Zink and Van Dyke, 2013). Furthermore, tendons, ligaments, joint capsule, bone, and articular cartilage all contain an important component called elastin. Elastin provides tissues with elasticity, which refers to the ability of a tissue to undergo reversible deformation. The amount of these components in different tissues varies greatly depending on the requirement for elasticity. Bone contains minimal amounts of elastin, while it is particularly

abundant within the ECM of structures that undergo repeated cycles of elongation and elastic recoil. Such structures with an abundance of elastin are joint capsules or the nuchal ligament. Elastic fibers are tremendously durable and can withstand up to a 200% increase in length from the resting state. With this stated, elastic fibers are capable of practically unlimited numbers of cycles of elongation and elastic recoil without loss of strength. Elastin is produced mostly during growth, but is also produced during the repair and remodeling phases of tissue healing.

Proteoglycans are glycosylated proteins that are components of ECM of all the connective tissues. The PGs consists of a core protein to which a number of glycosaminoglycan (GAG) side chains are covalently attached. The core proteins fluctuate greatly in length and amino acid sequence. Glycosaminoglycan side chains are long, linear polysaccharide polymers composed of repeating disaccharide units. There are several classes of PGs, but the PGs of most interest are the aggregating PGs and the small leucine-rich PGs (SLRPs). The aggregating PGs include, aggrecan, versican, brevican, neurocan, and are massive macromolecular complexes. Their high degree of hydration underlies the turgidity and resistance to compression in several tissues such as hyaline articular cartilage, meniscal fibrocartilage, and the nucleus pulposus of the intervertebral disk (Zink and Van Dyke, 2013). Small leucine-rich proteoglycans are associated with fibrillar elements of the ECM such as collagen and elastin and have many functions that include modulation of the assembly and interaction of collagen and elastin fibers, modulation of ion transport through the ECM, and regulation of growth factor effects on connective tissue cells (Zink and Van Dyke, 2013). The synthesis of PGs involves transcription and translation of a core protein, GAG conjugation of the protein, and secretion of the mature PGs into the extracellular environment. Existing PGs are degraded by a variety of proteases and polysaccharides. However, PGs bio-synthesis is a highly regulated anabolic process and can be

triggered by exposure of cells to a variety of biological mediators as well as some pharmacological agents.

INTRODUCTION TO OSTEOARTHRITIS

Cartilage strength and function depend on both the properties of the tissue and their structural parameters. As mentioned previously, cartilage is made up of macromolecules that are collagen and PGs (aggrecan) that are saturated with water. The interaction of the physical and biochemical structures of cartilage is necessary to allow the normal function of providing nearly frictionless motion, wear resistance, joint congruence, and transmission of load to subchondral bone. Chondrocytes are responsible for synthesizing and maintaining this material. Osteoarthritis (OA) can be defined as a disorder of the synovial joints. It is characterized by deterioration of articular cartilage, osteophyte formation and bone remolding, pathology of periarticular tissues including synovium, subchondral bone, muscle, tendon, ligament, and a low-grade, nonpurulent inflammation of a variable degree (Fox and Millis, 2010). OA occurs when there is disruption of normal cartilage structure and homeostasis, which results from a complex interaction of biochemical and biomechanical factors that occur concurrently and serve to perpetuate degradative change. The changes associated with osteoarthritis ultimately have an impact on the patient through decreased ability to use the joint or the production of pain, or both. Osteoarthritis affects any freely movable joints of small animals including the shoulder, elbow, carpus, hip, stifle, tarsus, and spinal articulations (Baltzer, 2008). It usually is not detected in the beginning state, because animals will hide their weaknesses as a survival technique. Unfortunately, once OA has begun, the progression of the disease can only be slowed but never completely stopped. Nevertheless, understanding the basic mechanisms involved in the development and progression

of OA provides a basis for establishing a reasonable expectation for the patient and a rational plan of treatment for this condition.

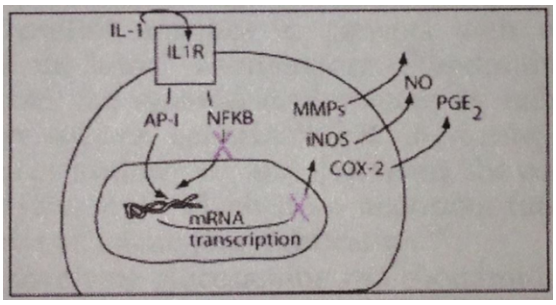
At the overt stage of the disease, OA chondrocytes produce higher levels of matrix metalloproteinases (MMPs) and lower levels of cartilage matrix molecules than healthy chondrocytes (Henrotin et al., 2004). Due to the imbalance between catabolic and anabolic processes from the chondrocytes, cartilage loss in osteoarthritis occurs as a consequence of enzymatic degradation of the ECM, resulting in loss of PGs (aggrecan) and cleavage of type II collagen (Neil et al., 2005). Matrix metalloproteinase has many different substrates that are similar in structure, but their actions on type II collagen differ. For instance, the triple helical region of the type II collagen molecule is resistant to degradation by most proteinases, but can be cleaved by the action of collagenases (MMP-1, -8, and -13) (Neil et al., 2005). Afterwards these collagen fragments proteins are susceptible to being broken down into smaller protein fragments by gelatinases (MMP-2 and -9), which are enzymes that can also degrade aggrecan (Neil et al., 2005). Furthermore, stromelysins (MMP-3, -10, -11) are capable of degrading aggrecan directly, type II collagen directly from the beginning of this process, and small PGs of the ECM (Neil et al., 2005). Overall, these multiple members of the MMP family are acting together and are responsible for the degradation of the collagen fibrils. The MMPs are zinc-dependent proteinases involved in the normal physiologic turnover of cartilage (Neil et al., 2005). The MMPs have naturally produced inhibitors termed tissue inhibitors of metalloproteinases (TIMPs) that help regulate MMP activity. However, in an osteoarthritic joint, the production of TIMPs is insufficient to control increased MMP activity that has been discussed above.

Aggrecanases appear to be the principal mediators of aggrecan degradation. Their activity results in the release of core protein and GAG constituents of aggrecan into synovial fluid (Neil

et al., 2005). The GAG fragments have been used as markers of cartilage loss in osteoarthritis. Aggrecanases, like MMPs, are metalloproteinases and can be inhibited by TIMPs (Neil et al., 2005). Martel-Pelletier et al., (2005) states that aggrecans are probably among the first cartilage matrix constituents to be affected, as they are progressively depleted in parallel with the severity of the disease. A decrease in aggrecan glycosaminoglycan content in the ECM can result in over compression of the cartilage under load, causing an adverse response by the chondrocytes with increased protease secretion and subsequent tissue degeneration.

Osteoarthritis is also associated with increased concentrations of other inflammatory mediators such as nitric oxide and prostanoids, particularly prostaglandin E2 (PGE2). Nitric oxide induces a number of pathophysiologic events characteristic of OA, including enhanced MMP synthesis and reduced synthesis of interleukin-1 receptor antagonist (IL-1Ra), proteoglycan, and type II collagen (Neil et al., 2005). Prostaglandin E2 is found in the synovial fluid of animals with OA in increased concentrations, because arachidonic acid increases within the joint and is the precursor of PGE2. Prostaglandin E2 has actions of vasodilation and cartilage PG depletion. Furthermore, Neil et al., (2005) states that central to the induction of degradative enzyme and inflammatory mediator synthesis in OA tissues are a number of cytokines, the most important of which is interleukin-1 (IL-1). Cytokines appear to be first produced by cells of the synovial membrane and later by activated chondrocytes. Interleukin-1 pathway (figure 1) mediates its effects on chondrocytes through a cell membrane-associated interleukin-1-receptor (IL-1R) (Neil et al., 2005). The IL-1 binds with IL-R and induces production of transcription factors, such as activator protein-1 and nuclear factor kappa B. These transcription factors then bind to binding sites of promoters of various genes and increases their transcription, including genes such as MMP's, inducible nitric oxide synthase, and cyclo-oxygenase-2. In general, IL-1

acts to enhance cartilage degeneration and inhibit repair. Additionally, besides cartilage degradation the synovial membrane and subchondral bone show structural changes. Subchondral bone thickening is accompanied by increased osteoid volume and a low mineralization, suggesting that a dysregulation of bone remodeling may be part of OA (Henrotin et al., 2005).



(Figure 1) Chondrocyte cell and the interleukin-1 pathway

DIAGNOSIS AND TREATMENT OF OSTEOARTHRITIS

Multiple etiologies can contribute to the formation of OA, including defective articular cartilage structure and biosynthesis, joint trauma, joint instability, congenital and developmental abnormalities, and inflammatory conditions (Aragon et al., 2007). Osteoarthritis affects approximately 1 in 5 adult dogs in the U.S. (Fox and Millis, 2010). It is the number one cause of chronic pain in dogs, and approximately 10-12 million dogs in the U.S. show signs of OA (Fox and Millis, 2010). When looking for signs of feline OA it is particularly challenging for owners and veterinarians to identify, purportedly because signs such as overt lameness that is noticed in dogs is rare in cats (Klinck et al., 2012). Furthermore, feline radiographic images do not correlate well with expressed pain or functional impairment, thereby hindering diagnosis and therapy (Klinck et al., 2012). Radiographic images are used to help diagnosis OA in companion animals and consist of advanced images, such a computed tomography, magnetic resonance imaging, and nuclear scintigraphy. Along with radiographs a proper diagnosis depends on a complete history and full assessment of the patient including: a complete physical, orthopedic,

and neurologic examination, advanced gait analysis, clinicopathologic examination, electrodiagnostic testing, muscle biopsy examination, and special tests (Fox and Millis, 2010). The special tests include: muscle percussion, serology for pathogens, measurements of acetylcholine receptor antibody, immunohistochemistry, and molecular diagnostic techniques (Fox and Millis, 2010). After diagnosing an animal with OA the management of OA typically involves a multimodal approach, which can include one or more of the following: activity control, weight management, nutritional support, physical therapy, administration of nonsteroidal anti-inflammatory drugs, analgesic medications, nutraceuticals, and in some cases surgery (Aragon et al., 2007).

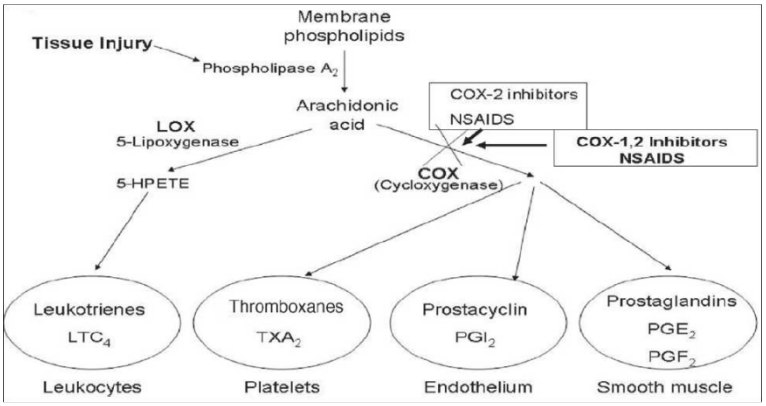
MEDICINAL MANAGEMENT

Medicinal management include several nonsteriodal anti-inflammatory drugs (NSAIDs), polysulfated glycosaminoglycan (PSGAG), hyaluronic acid, and several corticosteroids, including betamethasone, dexamethasone, triamcinolone, methylprednisolone and prednisolone (Lees, 2003). These are available in products with veterinary marketing authorizations for intravenous, intramuscular, oral and local (intra-articular) administration (Lees, 2003). Nonsteroidal anti-inflammatory drugs are effective for managing acute and chronic orthopedic pain as well as post-surgical pain (KuKanich et al., 2012). Currently, several NSAIDs (carprofen, cinchophen, deracoxib, etodalac, firocoxib, flunixin, ketoprofen, mavacoxib, tepoxalin, tolfenamic acid, and vedaprofen) have approval for the control of canine chronic pain (Fox, 2010). However, NSAIDs approved for feline use are far more limited (meloxicam, tolfenamic acid, ketoprofen, robenacoxib, carprofen, and aspirin) and short administration of them depends on the country (Fox, 2010). There are not as many NSAIDs for feline use due to the potential risk of NSAIDs toxicity in cats. Cats are susceptible to NASIDs toxicity, because of slow

clearance and dose-dependent elimination. They have a low capacity for hepatic glucuronidation of NSAIDs, which is the major mechanism of metabolism and excretion for this class of drug (Fox, 2010). However, many clinicians manage the exclusive pain of OA in dogs simply by sequencing different NSAIDs until satisfactory patient results are found or unacceptable adverse reactions are experienced (Fox and Millis, 2010).

The goal of NSAIDs is to inhibit PG formation that contributes to clinical signs and pathways of OA, while sparing PG production associated with beneficial physiological functions. This goal is achieved through NSAIDs manifesting their mode of action on the arachidonic acid (AA) pathway (figure2). The AA pathway produces a number of different eicosanoids, known as signaling molecules that exert control over many bodily systems, mainly in inflammation, or immunity, and as messengers in the central nervous system. There are four families of eicosanoids: the prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Two enzymes catalyze fatty acid oxygenation to produce these eciosanoids. One of the enzymes is cyclo-oxygenases (COX) which generate prostaglandins, prostacyclins, thromboxanes, and are referred to as prostanoids. Furthermore, the other enzyme lipoxygenase generates leukotrienes. Normally, in the body, prostaglandins, specifically PGE2, have many beneficial roles, but during the progression of OA PGE2 takes on a more damaging role. Some of those damaging roles of PGE2 include: lowering the threshold of nociceptor activation, promoting synovitis in the joint lining, enhancing the formation of degradative matrix metalloproteinases, and depressing cartilage matrix synthesis by chondrocytes (Fox and Millis, 2010). In contrast, some of the beneficial roles of PGE2 are; enhancing platelet aggregation to prevent excessive bleeding, maintaining integrity of the gastrointestinal tract, and facilitating renal function (Fox and Millis, 2010). Certain NSAIDs act to inhibit both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2

(COX-2) (eg. aspirin, ketoprofen, ketorolac) while other NSAIDs preferentially inhibit COX-2 or are COX-1 sparing in various degrees (eg. meloxicam, carprofen, etodolac, tolfenamic acid) (Mathews, 2002). These two enzymes are what cause beneficial and damaging roles that have been described above. COX-1 is responsible for the beneficial roles of PGs and COX-2 is responsible for the damaging roles of PGs. KuKanich et al., (2012) describes a COX-1/COX-2 inhibitory ratio, also known as the IC50 ratio, which is defined as the concentration of the drug (NSAID) needed to inhibit the activity of both enzymes COX-1 and COX-2 by 50%. This ratio has a high concentration of NSAID before causing 50% inhibition of COX-1 and a low concentration of NSAID to reach the IC50 for COX-2 (Fox and Millis, 2010). Therefore, the higher the numerator and lower the denominator the higher the absolute value is in creating a greater COX-1/COX-2 ratio. Thereafter, a greater COX-1/COX-2 ratio theoretically will create a more optimal performing NSAID (Fox and Millis, 2010). However, animals that have been administered NASIDs may have adverse effects that occur in the gastrointestinal tract (GI), in the kidneys, or the liver.



(Figure 2) Arachidonic Acid pathway

Nonsteriodal anti-inflammatory drugs can irritate the GI mucosa directly when administrated orally or following secretion in bile regardless of administration type because

many NSAIDs are weak acids. Gastrointestinal adverse effects can range from vomiting, anorexia and diarrhea to mild gastritis and severe gastrointestinal ulceration, bleeding and death (KuKanich et al., 2012). Prostaglandins E2 and prostacyclin I2 (PGI2) have important gastro-protective effects including mucosal blood flow, increased mucus production, increased bicarbonate production, decreased acid secretion and increased turnover of gastrointestinal epithelial cells (KuKanich et al., 2012). A domino effect occurs through the inhibition of both COX-1 and COX-2, which affects PGE2 and PGI2, which then causes adverse GI tract effects within an animal.

In contrast to inhibition of both COX enzymes, it has been suggested that inhibition of COX-1 or COX-2, exclusively, results in minimal GI adverse effects (Wallace et al., 2000). This suggestion is thought to be due to an up-regulation of the COX enzyme that is not being inhibited since both COX-1 and COX-2 produce PGE2. Furthermore, it appears that recently licensed veterinary NSAIDs have a decreased frequency of GI tract adverse effects in dogs compared to drugs such as aspirin, ketoprofen, phenylbutazone, tolfenamic acid, and flunixin (Reimer et. al., 1999; Nishihara et. al., 2001; Luna et. al., 2007). A study on research dogs was conducted for 90 days and results concluded that ketoprofen, flunixin, and etodolac produced greater gastric lesion scores than the placebo (lactose), carprofen, and meloxicam (Luna et al., 2007). Moreover, another study observed greater GI lesions after aspirin administration compared to carprofen and etodolac in healthy experimental dogs (Reimer et al., 1999). With that said, it is also believed that some NSAID drugs may lose the COX-1 sparing effect at high doses and the frequency of GI tract adverse effects will increase (Peterson and Cryer, 1999). A study conducted using the NSAID etodolac at higher doses caused GI lesions (2.7x label dose) or death (5.3x label dose) (KuKanick et al., 2012). Similarly, in another study meloxicam has also

been associated with GI toxicity at higher doses (Reed, 2002; Enberg et. al., 2006). In addition to GI adverse effects animals may also experience adverse effects of the kidneys.

Prostaglandin E2 and PGI2 also aid in some normal functions of the kidneys. Prostaglandin E2 and PGI2 alter kidney physiology by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport (Simmons et al., 2004). They also stimulate renin release and alter total renal blood flow and regional blood with the kidneys of dogs (Simmons et al., 2004). Furthermore, studies have suggested that high doses of NSAIDs, sodium depletion, hypotension (decreased or low blood pressure), hypovolemia (reduction in volume of blood), and anesthesia appear to increase the risks of renal adverse effects. Data et al., (1976), conducted a study examining the impact of high doses (6x dose label) of aspirin on renal blood flow. The results suggested that the predominant acute effects of aspirin on the kidneys were a decrease in total renal blood flow and altered distribution of renal blood flow within the renal cortex. Another study was conducted on hypovolemic dogs with high doses of aspirin (100 mg/kg) compared to hypovolemic dogs without aspirin treatment. Hypovolemic dogs treated with high doses of aspirin had a significantly decreased total renal blood flow and the distribution of blood flow in the cortex was decreased in all areas (Papich, 2007). In contrast, dogs without aspirin treatment only had a slightly decreased total renal blood flow, but distribution of blood flow was markedly altered with increased blood flow to the regions of the cortex closest to the medulla (Papich, 2007). Other studies have examined the effects of meclofenamate (a nonselective COX inhibitor), nimesulide (a COX-1 sparing NSAID), indomethacin (a nonselective COX inhibitor), carprofen (a COX-1 sparing NSAID), ketorolac (a presumptive nonselective COX inhibitor in dogs), and ketoprofen (a nonselective COX inhibitor) on the renal physiology of dogs. Meclofenamate significantly decreased renal blood flow and

altered redistribution of renal blood flow within the renal cortex during renal hypotension in dogs (Opgenorth et al., 1987). In contrast, a separate study Rodrı´guez et al., (2000) also administered meclofenamate and observed decreased renal blood flow without alteration of glomerular filtration rate in dogs, suggesting that glomerular filtration rate is not an appropriate indicator of acute NSAID induced renal effects. Nimesulide had minimal effects on renal blood flow in normal dogs, but dogs that were sodium depleted experienced a significant decrease in renal blood flow again without significant effects on the glomerular filtration rate (Rodrı´guez et al., 2000). Indomethacin, administered to anesthetized dogs significantly decreased renal blood flow and decreased sodium excretion, but had no effect on the glomerular filtration rate (Feigen et al. 1976). Another study by Frendin et al., (2006) studied the effects of NSAID carprofen on renal blood flow in anesthetized animals. The treatment of carprofen significantly decreased renal blood flow during anesthesia (about 50% compared to pretreatment values). Lastly, Lobetti et al., (2000) conducted a study using carprofen at 4 mg/kg, ketorolac at 0.5 mg/kg, and ketoprofen at 1 mg/kg were compared to morphine at 0.1 mg/kg in 40 dogs undergoing ovariohysterectomy. This study did not measure renal blood flow, but the NSAID treated dogs experienced significant effects manifested by decreased renal sodium excretion compared to baseline values. Overall, these studies have shown that animals are at higher risk of renal adverse effects during the administration of high doses of NSAIDs, sodium depletion, hypotension (decreased or low blood pressure), hypovolemia (reduction in volume of blood), and during anesthesia. However, healthy dogs administered approved doses of NSAIDs are at low risk for renal adverse effects (KuKanick et al., 2012).

Lastly, NSAIDs adverse effects in the liver have the lowest percentage of occurrence at 14%, while reactions in the GI tract are 64% and in the renal system are 21% (Fox and Millis,

2010). Adverse effects of NSAIDs on the liver can be divided into two groups; dose-dependent toxicity and dose-independent toxicity (Mensching and Volmer, 2009). Dose-dependent toxicity for example occurs within an animal due to massive overdosing of NSAIDs and dose-independent toxicity typically occurs within an animal that is administered the correct label dose of NSAIDs. One NSAID called firocoxib has been associated with fatty liver changes in young dogs at high doses (KuKanick et al., 2012). Another study investigated adverse effects of long term administration of several different NSAIDs (carprofen, etodolac, flunixin, ketoprofen and meloxicam) in dogs (Luna et al., 2007). This study concluded only minor and clinically insignificant changes occurred in serum biochemical variables. Another study evaluated the long term effects of NSAIDs on 805 client owned dogs of different breed, ages and body weight. Carprofen was administered for 84 days and 3.2 % of the dogs left the study due to adverse liver effects, with the majority leaving within the first 3 weeks (Mansa et al., 2007). MacPhail et al., (1998) suggested that most NSAID-associated hepatopathies occur within the first 3 weeks of treatment. Lastly, KuKanick et al., (2012) reported that long-term administration of firocoxib to 1002 dogs with OA was well tolerated with only 5% of dogs leaving the study due to adverse effects of any kind. These studies suggest that long-term NSAID administration is not associated with hepatocellular toxicity. However, these studies are the basis of recommendations for more intensive monitoring during the early stages of NSAID administration (KuKanick et al., 2012).

Another concern to be aware of is there are very few studies describing the use of NSAIDs in animals with underlying hepatic disease and no data indicating that animals with hepatic disease are at an increased risk of NSAID hepatic toxicity (KuKanich et al., 2012). However, animals with underlying hepatic disease may have decreased excretion ability of NSAIDs from the body since NSAIDs are primarily eliminated by hepatic mechanisms, but this

may be drug and disease specific (KuKanich et al., 2012). Holazo et al., (1985) and Brater and Lasseter, (1989) conducted a study in humans with liver dysfunction due to hepatic cirrhosis compared to healthy individuals. They stated that the elimination of carprofen and etodolac were not altered in either study group. However, it is unclear if similar pharmacokinetics of carprofen or etodolac occur in dogs with and without liver disease (KuKanick et al., 2012). With this stated, it is unclear if the dose of an NSAID needs to be decreased for an animal with pre-existing hepatic disease. Prior to instituting any NSAID drug or any other medicinal therapy a complete medical examination and physical examination has to be conducted. It is prudent to determine baseline renal and hepatic panels by clinical chemistries before administration of any drug, which is then followed up by repeat testing within two weeks and periodically after that. These periodic tests will inform the veterinarian of trends as well as absolute values and any unexplained increase in renal or hepatic enzymes. Along with NSAIDs, PSGAG and corticosteroid products are also medicinal drugs used to help the symptoms of an animal with OA.

A polysulfated glycosaminoglycan is considered to be a disease modifying osteoarthritic drug. Polysulfated glycosaminoglycans have been stated to protect articular cartilage from degradative enzymes as well as stimulate chondrocytes to produce normal components of articular cartilage (Baltzer, 2008). Specifically, Adequan is a PSGAG drug that is commercially available for animal use. The licensed PSGAG Adequan has been reported to be most effective when administrated in the early stages of OA. The reason for administrating this drug during the early stages of OA is to delay medically-aggressive treatment as long as possible during the progression of OA (Fox and Millis, 2010). Overall, PSGAG activity reduces proteoglycan degradation through inhibiting synthesis and activity of aggrecanases, MMPs, nitric oxide, and

PGE2, stimulates GAG synthesis through chondrocytes, and increase hyaluronan concentrations by synovial membrane cells (Fox and Millis, 2010). Therefore, PSGAGs are characterized as being a disease modifying or chondroprotective OA drug.

Another medicinal drug that is given to OA patients are corticosteroids. Corticosteriods are steroids that can be administrated orally or through injection. However, steroid injection in dogs is usually reserved for severe cases that have become non-responsive to other treatments and the animal is suffering and its quality of life is an issue (Henrotin et al., 2005). However, in contrast an in vivo study has suggested that corticosteroids have been shown to have a prophylactic effect on OA lesions, suggesting that they could also be used earlier in the disease process (Pelletier et al., 1989). In this study, twenty-four dogs had their anterior cruciate ligament (ACL) surgically sectioned. Six were treated with oral prednisone, 6 were treated with intra- articular injections of triamcinolone hexacetonide, at surgery and 4 weeks later, and tweleve dogs received no treatment. Results from this study indicated that untreated dogs developed significant cartilage lesions with prominent osteophytes, while operated dogs treated orally or with intra-articular injections had a significant reduction in osteophyte size. Cartilage erosions were observed in 25% of the untreated dogs, 8% of the dogs receiving oral prednisone, and none of the dogs receiving intra-articular triamcinolone hexacetonide. Therefore, corticosteroids significantly reduced the severity of OA structural changes of the cartilage in animals with surgically induced ACL injuries.

NUTRACEUTICAL MANAGEMENT

Another approach to the treatment of OA is through the use of nutraceuticals. The North American Veterinary Nutraceutical Council defines nutraceuticals as a nondrug substance that is produced in a purified or extracted form and administrated orally to provide agents required for

normal body structure and function with the intent of improving the health and well-being of animals (Bauer, 2001). There are more than thirty products that have been listed as being potentially beneficial for OA patients. Next to NSAIDs management, the uses of nutraceuticals are one of the fastest growing groups of health care products for human and animal use. The main nutraceutical compounds of interest are glucosamine (GlcN), glucosamine hydrochloride, glucosamine sulphate, chondroitin sulphate, and a combination of glucosamine hydrochloride and chondroitin sulfate.

Glucosamine is an amino sugar that is essential for the biosynthesis of glycosylated proteins and lipids. It also is a major constituent of extracellular matrix macromolecules such as glycosaminoglycans, glycolipids, and glycoproteins in its acetylated form, and is present in high quantities in articular cartilage, intervertebral disc, and synovial fluid (Henrotin et al., 2012). A primary theory suggested that when an exogenous form of GlcN is supplemented it provides the body with building blocks that are lacking for the synthesis of GAGs by chondrocytes. Various studies however have concluded that GlcN causes a reduction in proteoglycan degradation and inhibition of the synthesis and activity of degradative enzymes and inflammatory mediators such as aggrecanases, MMPs, nitric oxide, and PGE2 (Sandy et al. 1998; Fenton et al., 2002; Bryon et al., 2003). Furthermore, anabolic effects are limited to stimulation of GAG and proteoglycan production in aggrecan, but do not affect type II collagen (Busci and Poor, 1998). Furthermore, two in vitro studies concluded that high doses of GlcN may have detrimental effects on chondrocytes viability (Anderson et al., 1999; de Mattei et al., 2002). Ilic et al., (2003) also concluded that long-term exposure of GlcN had no detrimental effect on chondrocyte metabolism. However, another in vitro study administrating high doses of GlcN Fenton et al., (2000) failed to observe effects on chondrocyte viability, but concluded that a protective action

against cytokine-induced catabolic effects was maintained. Other studies Gouze et al., (2002); Largo et al., (2003) have also concluded that GlcN has a protective action against cytokine-induced catabolic effects, specifically by reduction in transcription factors involved in the intracellular signaling of IL-1. Transcription factors activator protein-1 and nuclear factor kappa B increase in cartilage during OA and these two factors stimulate the transcription of genes that play a vital role in cartilage degradation, such as COX, inducible nitric oxide synthase, and MMPs. Glucosamine appears to inhibit nuclear factor kappa B transcription activity and nuclear translocation, but has no effect on activator protein-1 (Largo et al., 2003). Furthermore, Gouze et al., (2002) concluded that glucosamine increases the expression of a decoy receptor that reduces binding of IL-1 to its receptor. Thus, the actions of glucosamine appear to have an anti-catabolic potency seen by its inhibition of the expression or activity of catabolic enzymes that are unregulated by OA.

In the body GlcN normally is in the form of glucosamine-6-phosphate, but GlcN is commercially available in four forms: glucosamine hydrochloride, glucosamine sulfate, N-acetyl-D-glucosamine, and a combination of glucosamine hydrochloride and chondroitin sulfate. The type of formulation of GlcN influences the activity, with glucosamine hydrochloride and glucosamine sulfate inhibiting cartilage degeneration more consistently than N-acetyl-D-glucosamine in vitro (Fox, 2010). When comparing GlcN to chondroitin sulfate the mechanism of action is similar, but not identical. Chondroitin sulfate also stimulates GAG synthesis and inhibits degradative enzyme synthesis, including MMPs (Ronca et al., 1998; Orth et al., 2002). However, chondroitin sulfate effects PGE2 and nitric oxide production to a greater degree and chondroitin sulfate is unique in its ability to improve synovial fluid viscosity by increasing hyaluronic acid concentrations (Bassler et al., 1998). Furthermore, chondroitin sulfate inhibits

IL-1 induced type II collagen degeneration while GlcN does not. There have been several companion animal clinical trials and experimental models that used a combination of glucosamine hydrochloride and chondroitin sulfate. The results of two trials conducted on dogs, suggested a cartilage sparing effect due to a reduction in severity of OA lesions (Hulse et al., 1998; Lippiello et al., 2000). Results of another study conducted on dogs concluded both preventative and therapeutic effects in the experimental models of osteoarthritis (Canapp et al., 1999). Furthermore, two other studies showed improvement in clinical signs as well as synovial fluid variables, serum GAG content, and articular cartilage metabolism improved, therefore suggesting a more normal synovial environment (Hardingham, 1998; Johnson et al., 2001).

One can see that GlcN has produced various effects in different in vivo and in vitro models. Trials have been conducted under different conditions, with different formulations and dosages, showing a tendency to produce a protective effect on articular tissues. However, nutraceuticals being classified as a dietary supplement by the FDA are not subject to strict regulatory guidelines. Therefore, commercially available products may vary widely in terms of purity and quality. Russel et al., (2002) concluded that human over the counter products vary considerable in composition, and another study stated that greater than 84% do not meet the label claim (Adebowale et al., 2000). Furthermore, a combined product of glucosamine and chondroitin was studied (Ramey et al., 2002). Results stated that GlcN content was 86% and chondroitin sulfate content was 83.3% of the label claim. Products are often marketed with a guaranteed analysis, however only a few products consistently meet their label claim (Liang et al., 1999; Adebowale et al., 2000; Liang et. al., 2002). Veterinary product efficacy in vivo or in vitro studies are limited and claims of efficacy are often made on the basis of subjective methods of assessment, including testimonials by owners or clinical trials that have not been subjected to

peer review (Neil et al., 2005). However, despite this issue nutraceutical products continue to gain popularity.

Part of the attraction to nutraceuticals is their potential use as an alternative to other drugs such as NSAIDs that are currently used for OA management. A study reported that NSAIDs administration resulted in prompt reduction of clinical signs, but signs reappeared after cessation of treatment (Morreale et al., 1996). This study was compared with animals treated with chondroitin sulfate who showed a delayed onset of effectiveness, but had a greater duration of clinical sign reduction (3 months) after treatment with chondroitin sulfate had been stopped (Neil et al., 2005). With the evidence that certain nutraceuticals are relieving OA symptoms longer than NSAIDs and that there have been no serious or adverse effects reported with GlcN, further studying of these nutraceuticals could open a new horizon for OA patients. Furthermore, since there has not been any serious or adverse effects reported from randomized controlled trials of GlcN, there are still potential side effects that should be kept in mind. The first side effect that OA patients should be aware of is the possibility of having an allergic reaction, commonly called a shellfish allergy. GlcN is extracted from chitin contained in shellfish and could lead to an allergic reaction (Henrotin et al., 2012). Secondly, GlcN sulfate is administrated as a salt combined with NaCl, which provides up to 30% of the daily intake of salt (Henrotin et al., 2012). Also, this has to be taken into account, because Na and Cl could have an effect on blood pressure and renal function. Lastly, some human and animal studies have suggested that GlcN can affect glucose metabolism and it has been shown to induce insulin resistance (Henrotin et al., 2012). However, a recent report by a GlcN manufacturer has concluded that GlcN had no effect on fasting blood glucose levels, glucose metabolism, or insulin sensitivity at any oral dose level in healthy subjects, individuals with diabetes, or those with impaired glucose metabolism (Henrotin

et al., 2012). The lack of reported adverse effects could be due to the short duration of exposure, so further studies are warranted to determine the long term effects of GlcN. Therefore, until these trials are conducted OA patients that are diabetic or hypertensive should undergo treatment cautiously. Also, based on the fact that GlcN has low and rare adverse effects, it represents a viable option for the management of OA as a symptomatic slow-acting drug, but that administration should be discontinued if no significant effect is reported (Henrotin et al., 2012). Following medicinal and nutraceutical treatment, physical rehabilitation is another step to the multimodal treatment of OA animals.

PHYSICAL REHABILITATION MANAGEMENT

Traditional management of dogs with OA has included anti-inflammatory and analgesic drugs, changes in lifestyle, and surgical management. More recent advances in the management of OA include weight loss, therapeutic exercise, and physical modalities to reduce the severity of clinical signs and the reliance on medications to control pain and discomfort (Millis et al., 2005). Therapeutic rehabilitation helps reduce body weight if needed, increases joint mobility, and reduces pain through the use of low-impact exercises designed to strengthen supporting muscles, as well as building up daily function. A complete physical examination is necessary to develop a successful physical therapy regime. It should include a clinical orthopedic and neurological examination (Bockstahler, 2006). Each therapist involved in the physical therapy treatment should have a comprehensive knowledge of the clinical features and treatment of the underlying disease, and to avoid any aggravation of the symptoms by inadvertently selecting inappropriate methods.

The weight of an OA animal should be addressed, because obesity in humans and animals is strongly associated with the development of OA. Obesity is a likely contributor to the

progression of OA, due to the immense exertion put on joints, tendons and ligaments. Weight reduction of 11% to 18% of the initial body weight of obese dogs resulted in significant improvement of hind limb lameness associated with hip OA in one study (Millis et al., 2005). To achieve weight reduction, treats should be eliminated from the diet along with implementing a special formulated prescription diet. In general, the weight reduction goal is to reduce fat composition to 20-25% of an animal's total body weight (Millis et al., 2005). The weight loss program and physical therapy should be started at the same time. The success of therapy will greatly depend on setting up an exercise program individually designed for the animal and its owner.

There are various types of physical exercises that are used to create a physical therapy program to reach the goals of weight loss and to increase mobility and strength. Some examples of exercises used are: slow leashed walks, walking or jogging, stair climbing, sit to stand exercises, and additional use of balance board, swiss balls, and physiorolls (Bockstahler, 2006). These programs also use various exercise equipment: balancing boards, swiss balls, and physiorolls. Perhaps the most important exercise equipment that can be implemented is the use of an underwater treadmill, because the physical properties of water can be utilized for the physical therapy. The body bears less weight in water and permits a pain free and more comfortable movement of joints and the water resistance is useful for muscle strengthening and cardiovascular training (Bockstahler, 2006). However, the most recommended exercise for dogs is to take several short walks throughout the day rather than one long forced walk. By doing this you can assess how long the animal can exercise without feeling pain. The daily exercise period can be increased by 10% per week. If the animal starts to experience pain while exercising, the exercise rate has to be reduced by at least 30%. In general, cats can gain advantages from

physical therapy, but the treatment protocol needs to be adapted to the behavior and handling potential. For example, the motion exercises should involve their natural play instinct, such as playing with a toy or laser pointer. For the most part therapies like range of motion exercises and stretching can be performed on cats, and massaging is also well accepted by them (Bockstahler, 2006). Before an animal starts any of these exercises thermotherapy (the use of warming agents and cryotherapy (the use of cooling agents) should be conducted along with massaging of the joints. The use of warming agents on OA tissue promotes blood to flow to the area, promotes tissue and collagen extensibility, decreases pain and muscle spasms, and joint stiffness (Millis et al., 2005). Heating agents that can be used are moist or dry hot packs, circulating warm water blankets, warm baths for distal joints (toes, carpus, tarsus, stifle or elbow), or therapeutic ultrasound (US) for heating of deeper joints (hip, shoulder, or vertebral joints). Most therapeutic ultrasound equipment currently offers two frequencies: 1 MHz (low-frequency) and 3 MHz (high-frequency) and two modes of utilization are possible: continuous and pulsated. Therapeutic ultrasound has four important biological properties and therapeutic effects. Ultrasound waves can penetrate biological tissue 5 cm in depth and can increase tissue temperature from +1 - +4 degrees Celsius. They also have effects related to their vibratory properties, which results in micro-massages that modify membrane permeability stimulating angiogenesis, increasing the release of growth factors, and promoting the proliferation of fibroblasts and collagen production (Sawaya, 2007). Lastly, ultrasound waves increase skin permeability, which encourages the passive diffusion of drugs into deep tissue (Sawaya, 2007). Cryotherapy is used to decrease blood flow, reduce inflammation, and slow metabolic rate (Millis et al., 2005). The cooling agents that can be used are cold packs or ice wrapped in a towel. The administration of a cooling agent can also be used during an exercise if inflammation is detected to prevent swelling and

pain. Massaging of the osteoarthritic area is important in both warm and cooling down period, because it aids in the release of muscle tension, improves blood and lymphatic circulation, and increases muscle flexibility. All hand grip massaging techniques, like stroking, kneading, or circulation pressure, which are well-known from classical human massage techniques, can also be used in companion animals (Bockstahler, 2006). Along with thermotherapy, cryotherapy, and physical therapy there are two other therapies that can be administrated that involve electrical stimulation.

The first that has been around the longest is called transcutaneous electrical nerve stimulation (TENS) used on companion animals. It is the most common method used in physical therapy and the two modalities that are currently used are called the gate control TENS and endorphinic TENS. Gate control TENS is, peripheral hyper-stimulation of large caliber sensitive fibers at high-frequency (generally 80 or 100 Hz, sometimes even 200 Hz for intense pain), which inhibits the transmission of pain influxes conveyed by small-caliber fibers in the dorsal horn of the spinal cord (Sawaya, 2007). The intensity of the current must remain beneath the threshold of motor neuron stimulation, which means it should not trigger muscular contraction. This type of current generates rapid, but short (one to several hours) analgesia, and is indicated mainly for acute and super-acute pain. Endorphinic TENS is stimulation of small-caliber fibers, at very low frequency (2 to 8 Hz), which favors the release of endorphins and encephalins in the encephalon (Sawaya, 2007). The current intensity is just above the muscular contraction threshold and provides gradual and longer-lasting pain relief (sometimes up to 8 hours). Endorphinic TENS is indicated for sub-acute and chronic pain. Another electrical stimulation therapy is called extra-corporeal shock wave therapy (ESWT) and is relatively a new physiotherapy treatment for canines. Good results in using ESWT have been reported by several

veterinarians, but the number of controlled clinical studies is still very limited (Bockstahler, 2006). This therapy uses very short waves emitted at low frequency and under very high pressure. These waves have very high energy and are characterized by a peak of very high overpressure (up to 100 times atmospheric pressure), followed by a trough, and occurs approximately within a microsecond. The theory behind ESWT mode of action is that short-term pain reduction may be based on a release of endorphins and long-term pain relief may be caused by mechanical and chemical effects on a cellular level where shockwaves can stimulate both the healing process and the modulation of pain signals (Bockstahler, 2006). It has been observed that ESWT is effective in reducing pain rapidly, has a sustainability (pain relieved from several weeks to months), and has improved mobility and quality of life for arthritic dogs (Sawaya, 2007). Furthermore, electrotherapy in general can be a possible treatment administrated to cats.

In the treatment of cats and dogs the involvement of the pet owner is especially important. In companion animals, especially those with chronic disorders, it is absolutely necessary to inform the owner that life-long treatment is often required along with a treatment plan. This is important, to improve the compliance of the owner and to clarify the prognosis of the treatment (Bockstahler, 2007). A lot of the physical exercises can be conducted at home, like some of the easy hand grip massages, range of motion exercises, and TENS therapy. It is imperative that the owner plays an active role for the success of the animal and that these treatments are compatible with the owner's work schedule. Furthermore, there most likely will have to be home environment modifications for the osteoarthritic animal if possible. Osteoarthritic animals show decreased daily functions like climbing stairs, jumping into the car, getting into bed, or using a litter box. Ramps or wider steps can be installed to aid with climbing into bed, vehicles, or litter boxes. During a cold season slippery grounds can often be an obstacle

for OA animals and the use of inexpensive carpeting can be a temporary solution. Whenever, possible animals should be moved from a cold, damp outdoor environment to a warm, dry inside environment. Their sleeping area should be soft and warm, but firm enough that the animal can get up easily. The use of a circulating warm-blanket under the blankets provides heat that may reduce morning stiffness. Pet owners may have more free time during the weekends and overdoing activities during the weekend should be avoided. Overall, good owner-education together with regular appointments in the clinic enables quick rehabilitation and improvement of the clinical signs in companion animals.

SUMMARY

Osteoarthritis is an important subject for companion animals, because of its prevalence in companion animals and its progressive nature. It has been noted that approximately 1 in 5 adult dogs in the U.S. are diagnosed with OA, approximately 10-12 million dogs in the U.S. show signs of OA, and it is the number one cause of chronic pain in dogs. However, cats are difficult to diagnosis because they are good at hiding signs of lameness in the veterinarian's office and also there is not a correlation between radiographic images and expressed pain or functional impairment. Osteoarthritis is a progressive disease that occurs from the imbalance of catabolic and anabolic metabolism within a joint and once homeostasis of the joint is disturbed there is no cure. Also, it is the most common form of arthritis in companion animals. Clinical signs in cats can be noticed at home by owners which may include; change of attitude (irritably, especially when touched in tender areas), sleeping or resting more than in the past, reluctance to groom, difficulty getting in or out of the litter box, and difficulty jumping up or down of furniture. Clinical signs in dogs can include; change of attitude (guarding a particular joint), slowing down of daily activity, refraining for using steps, limping, resting more, and stiffness

and lameness (more apparent after a nap or in the morning). The most optimal treatment for osteoarthritic animals is through a multimodal approach. That multimodal approach can be conducted through the use of: medicinal drugs (NSAIDs, PSGAG, and corticosteroids), nutraceuticals (different GlcN formulations), and physical therapy rehabilitation. All of these steps of treatment are important, especially beginning PSGAG and nutraceuticals early on in the progression of the disease, since they are most effective during the mild to moderate stages of OA. While a strict treatment regime will not cure the animal, it may help slow-down the progression and control the amount of chronic pain. Overall, the animal's quality of life is at heart and being able to improve it is every animal lover's wish.

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VITA

Graduate School
Southern Illinois University

Rebecca A. Cason

rcwildflower08@aol.com

Southern Illinois University Carbondale
Bachelor of Science, Animal Science Pre-Vet Specialization, May 2012

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