The pathophysiology and medical management of canine osteoarthritis

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ABSTRACT

Osteoarthritis or degenerative joint disease is a condition characterised by degeneration of articular cartilage often associated with the formation of new bone at joint surfaces or margins. Commonly encountered in dogs, osteoarthritis may have a gradual onset, but may also occur acutely. Osteoarthritis can be a primary disease of joint cartilage, but is more often secondary to abnormal stresses on joints. This article describes the pathogenesis and progression of cartilage degeneration as well as the dietary, lifestyle and pharmacological management of osteoarthritis. Recent pharmacological developments allow the clinician not only to control clinical signs of the disease, but also to slow the progression of cartilage degeneration.

Key words: canine, degenerative joint disease, management, osteoarthritis, pathophysiology.

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INTRODUCTION

Osteoarthritis (OA) is a disorder of movable joints characterised by degeneration of articular cartilage and the formation of new bone at joint surfaces or margins[3,26]. The term osteoarthritis indicates degenerative joint disease with concurrent synovial inflammation, which is not always present[3,26]. Degenerative joint disease is the the term preferred by many clinicians and indicates a pathological process not always associated with inflammation. Since osteoarthritis appears to be the term most commonly used in the veterinary literature, we have chosen to use it throughout this article. In the majority of cases, OA presents as lameness, which may have a gradual onset but can flare up acutely after exercise[3,26]. Affected dogs are reluctant to perform normal activities such as climbing stairs. Lameness is exacerbated by rest but decreases after a few minutes of activity. Cold damp conditions, obesity and prolonged exercise often worsen signs of lameness[3]. OA is the most common joint disease affecting dogs[3].

PRIMARY AND SECONDARY OSTEOARTHRITIS

Primary OA is the result of defective articular cartilage structure and biosynthesis and is considered uncommon in dogs [3,5]. Primary OA often affects multiple joints and may be more common in certain breeds such as the chow, dalmatian and samoyed[26].

Secondary OA results from abnormal stresses placed on normal articular cartilage or as a consequence of other joint diseases such as infection, osteochondrosis, crystal arthropathy or immune-mediated inflammation[3,5]. Abnormal joint stress is caused by damage to intra- and extra-articular structures that stabilise the joint, such as ligaments, muscles and the joint capsule[8]. Luxations, subluxations and abnormal joint conformation are also important causes of abnormal joint stress[3].

CARTILAGE DEGENERATION

Articular cartilage has a complex structure that is designed to absorb shock and to decrease friction. Joint cartilage is composed of a small number of chondrocytes embedded in a matrix synthesised by the chondrocytes themselves[8]. The matrix consists mainly of water and also contains collagen and proteoglycans. Proteoglycans form complexes with hyaluronic acid and act as osmotic traps that hold water between collagen strands[26]. The proteoglycan and water aggregates act as a shock absorber that enables cartilage to withstand normal loading forces[8]. Articular cartilage should be seen as a dynamic tissue, with chondrocytes constantly synthesising products that repair aged or damaged cartilage[8]. The current concept of OA is that catabolic processes exceed anabolic processes and that regeneration of cartilage becomes ineffective[8,31]. OA should not be seen as a static process involving excessive wear and tear on cartilage but as an active process that inhibits normal cartilage regeneration. The end result of this process is the loss of cartilage proteoglycans and an abnormal cartilage structure[8,26]. This occurs despite an initial increase in chondrocyte proteoglycan synthesis. However, this proteoglycan has an abnormal biochemical structure and is more easily extracted from cartilage[26]. As cartilage degeneration progresses, proteoglycan and hyaluronic acid content decreases[8]. The reduction in proteoglycan, hyaluronic acid and to a lesser extent collagen is due to breakdown by catabolic enzymes liberated during early OA[26]. There are 4 major groups of enzymes involved in cartilage degradation: aspartic proteinases, cysteine proteinases (cathepsin and others), serine proteinases and the metalloproteinases (collagenase, gelatinase, stromelysin and others)[15,26]. Prostaglandin E_2 also plays a role in cartilage catabolism[26]. These factors are produced by synovial cells and chondrocytes in response to a number of cytokines, including interleukin-1, interleukin-6 and tumour necrosis factor (TNF)[31,38]. The synovial microvasculature and membrane may also play an important role in the release of factors into the joint space[31]. Moderate to marked synovitis has been observed in 50 % of surgically resected synovial membrane specimens in dogs[3]. The high levels of TNF found within arthritic joints may increase leukocyte adhesion molecules on synovial vascular endothelium[4]. The influx of leukocytes and subsequent release of inflammatory substances may contribute to cartilage degradation[31]. These factors directly degrade collagen and proteoglycans and suppress chondrocyte synthesis of matrix substances[8].

In summary, an initial insult to the

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cartilage results in cytokine release and catabolic enzyme production. The enzymes cause direct damage to the cartilage and may influence proteoglycan synthesis by chondrocytes. The net result is cartilage with decreased load-bearing capacity and localised areas of softening[3]. Flaking and fissuring of cartilage occurs with resultant exposure of underlying bone[3].

MEDICAL MANAGEMENT OF OSTEOARTHRITIS

Weight reduction and controlled exercise

The control of obesity is absolutely essential in the management of OA[3,9]. Weight control alone can often completely control the clinical signs of OA[9]. The patient's body weight should be returned to normal or slightly subnormal, depending on age, breed and conformation. Weight reduction decreases mechanical stresses placed on joints and helps reduce the degenerative process[5].

Modification of patients' exercise is also important. Muscles, ligaments, tendons and joint capsules serve an important protective function that is enhanced in fit animals[3]. Strenuous high-impact exercise, such as running on a hard surface, can accelerate OA and may exacerbate clinical signs[5,9]. Low-impact exercise such as walking or swimming can strengthen joint supporting structures, improve patient well-being and stimulate the release of endorphins[5]. The intra-articular administration of endorphins was shown to have a marked anti-inflammatory effect in a canine model of OA[25]. OA may also cause hypertonicity of flexor and extensor muscles around the joint, resulting in decreased elasticity and further joint trauma[21]. Exercise routines should be individualised for each patient and adjusted according to clinical signs of pain and inflammation. Exercise should be performed daily, as activity limited to weekends will result in an unfavourable outcome[5]. Exercise routines should be initiated with short walks on a leash and then gradually increased until clinical signs appear[34]. The distance walked is then reduced until no worsening of clinical signs is observed. Swimming is excellent exercise and should be encouraged under close supervision. As in humans, the clinical signs of OA can worsen in cold, damp weather[34]. The provision of a well-padded warm bed can help alleviate some of the pain associated with OA. As OA progresses, the exercise routine should be shortened to accommodate ongoing cartilage degeneration[9].

Pharmacological management

Steroidal or nonsteroidal anti-inflammatory agents have been the mainstay of OA management[3,8,9]. It is important to note that these drugs do not alter the underlying pathophysiological process but merely control signs of pain and inflammation. Recent developments have allowed the use of drugs such as the polysulphated glycosaminoglycans that modify the underlying pathophysiological process. Complementary therapy such as essential fatty acid supplementation, green-lipped mussel extract, acupuncture and doxycycline administration may also be useful in the overall management of OA.

Nonsteroidal anti-inflammatory drugs

Joint inflammation, which is not present in all cases of OA, is initiated at the synovial membrane which provides cell wall phospholipids for arachidonic acid production[9]. Arachidonic acid is metabolised by the enzymes cyclo-oxygenase and lipo-oxygenase to produce a number of inflammatory substances such as the prostaglandins and leukotrienes[9]. Most nonsteroidal anti-inflammatory drugs (NSAID) inhibit cyclo-oxygenase and prevent synthesis of prostaglandins[12]. Recent evidence suggests that more than one cyclo-oxygenase enzyme is responsible for the production of prostaglandins. The cyclo-oxygenase isozyme II (COX II) found in cells associated with inflammation differs from cyclo-oxygenase I (COX I) found in most other cells[14]. Prostaglandins formed by COX I are considered cytoprotective[14]. For this reason a selective blocker of COX II would be more specific in treating inflammation, and not inhibit the potentially beneficial effects of prostaglandins produced by non-inflammatory cells. Certain newer NSAIDs recently marketed, such as meloxicam, claim to be specific inhibitors of COX II[14]. It is important to realise that NSAID have analgesic and anti-inflammatory properties and do not modify cytokine-mediated pathways that result in cartilage degeneration[8]. It has also been shown that most NSAID inhibit chondrocyte synthesis of proteoglycans directly, contributing towards the pathological process[12]. Some NSAID may not inhibit chondrocyte synthesis and are termed chondroprotective[12]. NSAID are also associated with other adverse effects including gastrointestinal ulceration and renal papillary necrosis[27]. Recent evidence indicates that NSAID-mediated production of tumour necrosis factor causes leukocyte adhesion to gastric microvascular endothelium with subsequent ulceration[1]. It appears that further study is indicated to determine the effects of NSAID-mediated tumour necrosis factor production on the pathophysiology of OA. Owing to their adverse effects, NSAID should only be used during OA-induced lameness and should be discontinued when the signs of OA are well controlled. If prolonged administration is necessary, then agents that protect against gastrointestinal ulceration should be considered. Synthetic prostaglandin E_1 (misoprostol) is the drug of choice to prevent NSAID-mediated gastric ulceration[29]. Histamine receptor (H_2) antagonists and proton-pump inhibitors are not as effective for this purpose[22]. Table 1 gives NSAID dosages recommended in dogs.

Aspirin

Aspirin (acetylsalicylic acid) was the 1st NSAID to be used in modern medicine and still enjoys widespread usage[27]. Aspirin is commonly recommended for the treatment of canine OA and is a readily available, inexpensive drug[9,19,34]. Studies have shown, however, that aspirin decreases chondrocyte production of collagen and proteoglycans and long-term use may enhance cartilage degradation[17]. Aspirin should only be used during OA episodes and once the disease is under control, therapy should be tapered down and discontinued if possible[19]. Gastrointestinal side-effects often occur with aspirin therapy and owners should be informed of the clinical signs of ulceration, which include vomition, anorexia, melaena and abdominal pain[29,39]. Misoprostol is very effective at preventing aspirin-induced gastric ulceration[29].

Phenylbutazone

Phenylbutazone can also be used in the management of OA and can provide better pain relief than aspirin[34]. As phenylbutazone selectively inhibits prostaglandin E_2, it may not be effective in all cases of OA, since other inflammatory mediators also play a role[9]. As well as having side-effects similar to the other NSAID, phenylbutazone can cause a dose independent idiosyncratic bone-marrow suppression[27]. Weekly blood cell counts should be considered during therapy.

Carprofen

Carprofen is one of the newer NSAID and has been evaluated for the management of canine OA[36]. Most dogs receiving carprofen showed a positive response with alleviation of clinical signs. The drug is associated with very few gastrointestinal and renal complications and even prolonged dosage regimens have failed to show significant adverse effects[36].

Table 1: **Dosage recommendations for NSAID in dogs.**

Generic drug name	Dosage recommendations in dogs	Available in South Africa	References
Aspirin	10 mg/kg bid[a] p/o[b]	Yes	26
Phenylbutazone	10 mg/kg bid p/o	Yes	3,26
Carprofen	1–2 mg/kg bid p/o	No	3,26
Piroxicam	0.3 mg/kg once every 48 hours p/o	Yes	3,26
Meloxicam	0.2 mg/kg sid[c] p/o for 7–21 days, thereafter 0.1 mg/kg	Yes	3,26
Ibuprofen	Not recommended for use in dogs	Yes	13
Tenidap	3 mg/kg bid p/o	No	15

[a]twice per day.
[b]per os.
[c]once per day.

Piroxicam

Piroxicam is used in osteoarthritic humans who have not responded to other NSAID[27]. This drug has no suppressive effects on chondrocyte synthesis and is considered chondroprotective[12]. The drug has been associated with severe gastrointestinal ulceration in dogs and should be used with concurrent anti-ulcerogenic therapy[32]. Lengthy dosage intervals makes this drug convenient for pet owners to administer.

Meloxicam

Meloxicam has been shown in experimental models of canine joint inflammation to have good anti-inflammatory effects[35]. Cytological analysis of synovial fluid after initiation of joint inflammation showed decreased leukocyte numbers in meloxicam-treated dogs . The same study, however, also showed decreased synovial fluid hyaluronic acid content in the meloxicam-treated group as compared to the placebo-treated group.

Ibuprofen

Ibuprofen is mainly used in human medicine and is freely available as an over-the-counter preparation. The use of ibuprofen is strongly discouraged in dogs owing to its potent ulcerogenic properties in this species[13,27]. The therapeutic dose is too close to the toxic dose for routine clinical use.

Tenidap

Tenidap is a new NSAID that has been evaluated in an experimental canine model of OA[15]. The drug is classified as an oxindole and inhibits cyclo-oxygenase and lipo-oxygenase[15]. It also modulates cytokine synthesis, inhibits leukocyte activity and decreases the synthesis and action of metalloproteinase enzymes. Oral administration of the drug immediately after induction of joint instability resulted in decreased cartilage degeneration, osteophyte formation and synovitis. Tenidap appears to modulate the underlying disease process. Further evaluation of this drug is needed before recommendations can be made.

Steroidal anti-inflammatory drugs

Glucocorticoids are potent anti-inflammatory agents with a mechanism of action that differs from the NSAID. Being lipid-soluble agents, glucocorticoids diffuse through the cell membrane, bind to the nucleus and induce the production of lipocortin[10]. Lipocortin has an anti-inflammatory effect by inhibiting phospholipase A_2 and preventing production of the prostaglandins and leukotrienes. It has also been suggested that corticosteroids are selective blockers of COX II[2]. Glucocorticoids affect most body systems and are associated with a number of adverse effects[10]. The joint cartilage is no exception and is also adversely affected [7]. The intra-articular administration of methylprednisolone in horses with no history of joint disease resulted in prolonged impairment of chondrocyte function[7]. Proteoglycan and collagen synthesis were inhibited for a 16-week period after a single injection[7]. The use of intra-articular corticosteroids is strongly discouraged[9]. Systemic glucocorticoid administration is controversial, with some authors stating that there is no place for systemic corticosteroids in the management of OA[8]. The general consensus is that corticosteroids should be avoided in the management of OA[3,8,9,26]. Corticosteroids may play a role when other treatments have failed but they should only be used for short-term management and discontinued if possible.

Polysulphated glycosaminoglycans, pentosan polysulphate and related agents

The introduction of the polysulphated glycosaminoglycans (PSGAG) and related agents has provided the possibility of treating the underlying pathogenesis of OA[20]. PSGAG and pentosan polysulphate have similar beneficial effects on the degenerating joint and a general description of the mechanism of action is applicable to both agents[16,20,30,33]. PSGAG are derived from bovine trachea and lungs and synthetically modified via the addition of sulphate groups. These negatively charged sulphate groups allow the drug to reach high concentrations in cartilage matrix[33]. Pentosan polysulphate is also synthetically sulphated but originates from plant-derived xylan[16]. The 3 major actions of the PSGAG are postulated to include the following:

1. Cartilage matrix synthesis is stimulated and chondrocytes produce increased amounts of proteoglycans. Synovial fibroblasts are also stimulated to produce hyaluronic acid. Hyaluronic acid increases the viscosity of synovial fluid and aids joint lubrication[16].
2. Cartilage degradation is prevented as metalloproteinases, complement, hyaluronidase and harmful enzymes released from leukocytes are inhibited[16].
3. Blood flow and perfusion of joint tissues and subchondral bone is increased[16]. This is a consequence of the antithrombotic, fibrinolytic and anticytokine properties of these agents[16].

These agents are considered very safe and the only significant adverse effect observed is their heparin-like action[20]. This can result in prolongation of the activated partial thromboplastin time (PTT), prothrombin time (PT) and activated coagulation time. They should not be administered to patients with bleeding tendencies, patients in shock or with a history of hypersensitivity[33].

Hyaluronic acid sodium has been used extensively for intra-articular administra-

Table 2: **Dosage recommendations for PSGAG and related agents in dogs.**

Generic drug name	Product available in South Africa	Dosage recommendations in dogs	References
Pentosan polysulphate sodium	Tavan SP 54 (Ethimed)	3 mg/kg s/c[a] or i/m[b] once per week for 4 treatments	16,30
Polysulphated glycosamino-glycan	Adequan IM (Luitpold Pharmaceuticals) Cosequin (Nutramax Laboratories)	5 mg/kg i/m every 4 days for 6 treatments Administer per os according to manufacturer's recommendations	5

[a]subcutaneously.
[b]intramuscular.

Table 3: **Alternative therapies for osteoarthritis in dogs**.

Generic drug name	Drug available in south africa	Dosage recommendation in dogs	References
Essential fatty acids	Derm Caps (DVM Pharmaceuticals)	Administered orally according to manufacturer's instructions	28
Green-lipped mussel extract	Green-lipped mussel extract (Compass Distributors)	Administered orally according to manufacturer's instructions	11
Doxycycline	Mildox (Centaur Laboratories)	2 mg/kg p/o[a] bid[b]	40

[a]per os.
[b]twice per day.

tion in osteoarthritic horses. Hyaluronic acid sodium was shown to be ineffective for the treatment of canine OA when administered intramuscularly[23]. Hyaluronic acid should therefore not be administered intramuscularly in dogs for the treatment of OA.

Routes of administration and dosages vary depending on the agent and formulation used[33,34]. PSGAG and related substance dosage recommendations in dogs are given in Table 2. As no comparative therapeutic trials have been performed in dogs, one agent cannot be recommended over another. Oral formulations have recently become available and are a convenient alternative to parenteral therapy.

Complementary therapy

A number of alternative therapies have been evaluated for the management of OA and have met with varying degrees of success. These therapies can be used when adverse side-effects of other drugs limit treatment applications or if pet owners seek natural or alternative therapies.

Essential fatty acids

Essential fatty acids that contain omega-6 or omega-3 fatty acids may be useful in decreasing inflammation associated with OA[6,28,37]. Omega-3 fatty acids are incorporated into phospholipid membranes and compete with other substances in the formation of leukotrienes and prostaglandins. Omega-3 derivatives are less pro-inflammatory than other lipid derivatives. One study showed an excellent response in 27 %, a good response in 32 %, and a poor response in 41 % of 22 dogs treated with essential fatty acids[28]. The dogs were treated for 2 weeks before results were evaluated. A longer course of therapy might have increased the percentage of dogs with a positive response[28].

Green-lipped mussel extract

The administration of green-lipped mussel (*Perna canaliculus*) extract has also met with a fair measure of success in managing canine OA[11,24]. The extract has been shown to have anti-inflammatory properties in various experimental models and also contains glycosaminoglycans[11,24]. The oral administration of this product for 8 weeks to 26 dogs with arthritis, alleviated clinical signs of lameness in a high percentage of cases[11]. The extract may also protect the gastrointestinal tract against NSAID-mediated ulceration[11]. Adverse effects reported in humans include transient increases in osteoarthritic pain, allergic reactions and gastrointestinal disorders[11].

Acupuncture

Acupuncture therapy has also been used for the management of human and canine OA[18,21]. In a clinical trial of 61 dogs with OA of various joints, 62 % of cases had an excellent to very good response[21]. The acupuncture points utilised are well described but this form of therapy should be performed by experienced veterinary acupuncturists[21].

Doxycycline

The oral administration of doxycycline has been shown to markedly improve OA lesions in an experimental canine model[40]. Doxycycline inhibits the activity of metalloproteinase enzymes by chelating divalent cations, such as zinc. The drug was administered prophylactically immediately after joint instability was surgically induced and has not been evaluated on joints with pre-existing degenerative changes. The use of doxycycline in the management of canine OA should be considered experimental until further clinical studies are performed.

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