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Pain management in dogs with osteoarthritis

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Smärthantering hos hundar med osteoartrit

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SAMMANFATTNING

Osteoartrit är en vanlig sjukdom hos våra domesticerade hundar och estimeras drabba tjugo procent av alla hundar över ett år. Tillståndet förknippas med kronisk smärta och nedsatt rörelsefunktion. Som behandling används ofta icke-steroida antiinflammatoriska läkemedel, så kallade NSAIDs med syfte att lindra smärtan och därmed förbättra livskvaliten. Även om NSAIDs har visat sig ha en stark smärtlindrande effekt associeras behandlingen även med ett flertal bieffekter som kan ge upphov till allvarliga skador relaterade till bland annat magtarmkanal och njurar. Dessutom är NSAIDs säkerhetsprofil för långtidsbehandling hos osteoartrit på hund ännu ej klarlagd.

Naturläkemedlena glukosmin- och kondroitinsulfat är idag ett vanligt supplement som ofta ges via maten. Dessa sägs kunna bromsa brosknedbrytningen i leden samtidigt som de stimulerar syntes av broskets extracellulära matrix (ECM). De sägs även ha en smärtlindrande verkan samtidigt som själva återuppbyggandet av leden också verkar smärtlindrande på sikt. De faktiska effekterna är dock omdebatterade och studier visar på olika resultat. NSAIDs tycks generellt nå bättre smärtlindrande effekt på kortare tid vilket gör att det finns skäl att ifrågasätta glukosamin- och kondroitinsulfat som enda behandling.

Fysisk rehabilitering och viktkontroll är också viktiga i behandlingen av osteoartrit hos hund. Överviktiga hundar löper större risk att drabbas av osteoartrit och den extra vikten försämrar även sjukdomstillståndet. En studie visade att hundar som fick begränsad fodergiva var mindre exponerade för utvecklandet och fortskridandet av osteoartrit.

Hundens situation bör även beaktas ur ett etiskt- och djurvälfärdsperspektiv. Osteoartrit är en livslång sjukdom och gränsen mellan när djurets lidande överskrider den effekt som nås med behandling är diffus. Enligt Djurskyddslagen skall ”djur skyddas mot onödigt lidande och sjukdom samt hållas och skötas på ett sådant sätt att det främjar deras hälsa och ger dem möjlighet att bete sig naturligt”. Hundar med osteoartrit har begränsad rörelseförmåga och är utsatta för smärtexponering till varierande grad. Det kan hända att vi bygger upp tolerans mot det tillstånd som hundar med osteoartrit befinner sig i och fortsätter behandla i lägen där det inte kan anses etiskt försvarsbart.

Syftet med denna uppsats är att diskutera behandling av smärta hos hundar med osteoartrit. Vilka risker finns det vid behandling med NSAIDs och skulle glukosamin- och kondroitinsulfat kunna vara ett alternativ? Vidare kommer vikten av viktkontroll att behandlas och den slutliga, till viss del obekväma frågan att ställas, när ska man respektive när ska man inte behandla?

SUMMARY

Osteoarthritis is a common disease in domesticated dogs and is estimated to affect twenty percent of all dogs over one year of age. The condition is associated with chronic pain and lameness. Non steroid anti-inflammatory drugs, also known as NSAIDs, are often used in the treatment of osteoarthritis and are known to relieve the pain and thereby improve the quality of life for those affected. Although NSAIDs are known to have a strong analgesic effect, the drugs are also associated with several adverse effects which can cause severe damage for example in the gastrointestinal tract and the kidneys. Furthermore NSAIDs safety profile for long-term treatment of osteoarthritis in dogs, is not yet fully elucidated.

The nutraceuticals glucosamine- and chondroitin sulphate are today common supplements to dogs, often mixed with the food. These are said to be able to slow down cartilage destruction in the joint while stimulating the synthesis of cartilage extracellular matrix (ECM). They are also said to have an analgesic effect. Its actual impact, however, is controversial and the two studies presented in this paper show somewhat different results. Both, however, agree that NSAIDs reach higher analgesic effect in less time, which means that there are reasons to question glucosamine and chondroitin sulphate as the only treatment in dogs with osteoarthritis.

Furthermore, physical rehabilitation and weight management play important part in the development and progression of osteoarthritis in dogs. Overweight dogs are more likely to suffer from osteoarthritis and the excessive weight also impairs the illness. One study showed that dogs who received limited amount of food over lifetime were less exposed to the development and progression of osteoarthritis than dogs in the control group.

It is important to care for the dogs even from an ethical- and animal welfare point of view. Osteoarthritis is a lifelong disease and the limit between when the animal's suffering exceeds the effect that can be reached with treatment, is diffuse. According to the Swedish Animal Welfare Act, “animals are to be treated well and to be protected from unnecessary suffering continuing to be managed in such a way that it promotes their health and allows them to behave naturally”. Dogs with osteoarthritis have limited mobility and are exposed to pain to varying degrees. There is a risk that we build up tolerance to the state of dogs with osteoarthritis and continue to treat them although it can’t be considered ethically defensible.

The purpose of this thesis is to discuss the treatment of pain in dogs with osteoarthritis. What risks are there in the treatment with NSAIDs and could glucosamine- and chondroitin sulphate be an option? Further, the importance of weight management will be addressed and the final, yet uncomfortable question to be asked, to treat or not to treat?

INTRODUCTION

Osteoarthritis is a painful condition that in a survey of two hundred veterinarians, has been estimated to affect as much as twenty percent of the dog population over one year of age (Pfizer Animal Health, 1996). There are numerous of strategies on how to treat osteoarthritis in dogs. They all have similar goals including giving adequate analgesic effect, preserve joint mobility by slowing down disease progression, and for some, even to improve the pathological condition by restoring the joint (McLaughlin, 2000).

However up till today there is no treatment that completely cure affected (KuKanich *et al.,* 2012). One of the main treatment methods is NSAIDs that act anti-inflammatory and analgesic but there is uncertainty about the safety profile, particularly in the long term. Treated dogs have been seen with adverse effects in the form of gastrointestinal-, kidney-, liver- and cardiovascular damage, to name the most common (KuKanich *et al.,* 2012). Henceforth NSAIDs just relieve the pain that dogs with osteoarthritis experience, without demonstrably improving the medical condition.

New methods have become popular in the treatment of osteoarthritis in dogs and one of them is the nutraceutical glucosamine, often combined with chondroitin sulphate. These are said to modulate the state of the disease whilst they also possess analgesic effects (Henrotin *et al.,* 2005).

As the dog gets older the joints successively wear out and this, along with obesity, have a major impact on the risk of developing osteoarthritis. Weight management and physical rehabilitation are considered cornerstones in the treatment by improving function and reducing the stress on the joints (Rychel, 2010).

Although the treatment methods are many, ultimately one may still end up in a dead end. The dog's suffering must be weighed against the effect you can actually achieve with the treatment, and sometimes it is ethically questionable how long the treatment should go on for.

The purpose of this thesis is to discuss the treatment of pain in dogs with osteoarthritis. What risks are there in the treatment with NSAIDs and could glucosamine- and chondroitin sulphate be an option? Further, the importance of weight management will be addressed and the final, yet uncomfortable question to be asked, to treat or not to treat?

MATERIALS AND METHODS

The search for literature emanated from the databases Web of Science, PubMed and Google Scholar. The keywords used for the searches were (dog OR canine), (osteoarthritis OR arthritis), (NSAIDs OR COX), (glucosamine AND chondroitin), (pain OR nociceptive), (weight management AND physical rehabilitation). These were used in various combinations to sort out and collect a number of articles. Some articles have also been found in reference lists of already chosen articles.

LITERATURE OVERVIEW

What is pain?

The official definition describes pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain, IASP; Läkemedelsboken, 2016). In other words, pain involves both sensory and emotional components and reflects, not only how the pain feels, but also how it makes you feel. Pain is an individual experience and can further be divided into nociceptive and neuropathic pain (Mathews *et al.,* 2014).

Nociceptive and Neuropathic pain

Nociceptive pain usually derives from tissue damage where nociceptors localised on free nerve endings, sometimes referred to as pain receptors, respond to chemical, thermal and mechanical stimulus. In addition there are algogenic substances such as histamine, bradykinin and prostaglandins, which through peripheral sensitization, enable and enhance pain perception (Attring *et al.,* 2002).

The peripheral nerves consist of myelinated and unmyelinated nerve fibres, propagating nerve impulses. They are headed to the dorsal horn of the spinal cord where a switch is made to ascending pathways, mainly to the thalamus. In the thalamus yet another switch is made to the sensory cortex and the limbic system. It is in the limbic system where both physical and mental pain become conscious pain (Attring *et al.,* 2002).

Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system (The International Association for the Study of Pain, IASP; Läkemedelsboken, 2016). It is a chronic type of pain which lesions can be widely varied and difficult to diagnose. The thing they have in common is all originate directly from the nervous system (Grubb, 2010).

Acute and Chronic pain

Pain can also be divided into acute and chronic. Acute pain is most often associated with tissue damage and usually occurs in dogs after a trauma, surgery, medical complications, infections or inflammatory diseases. The duration can vary from a few hours to several days. There is no subtle line where acute pain becomes chronic but traditionally pain that has been ongoing for more than three months is considered chronic pain (Mathews *et al.,* 2014).

Osteoarthritis is a complex chronic condition involving nociceptive- and possibly neuropathic pain. According to Dimitroulas *et al.* (2014), a neuropathic pain component may be predominant in individuals with minor joint changes.

Osteoarthritis in dogs

Johnston (1997) describes osteoarthritis as a syndrome rather than a single disease consisting of progressive and degenerative pathological changes regarding the synovial joint leading to pain and disability. A more detailed description made by Goldring & Goldring (2007) characterizes the condition as degeneration of the articular cartilage, changes in the peri-articular and subchondral bone with osteophyte formation and limited intraarticular inflammation with synovitis.

In dogs osteoarthritis occurs mainly secondary to congenital or acquired musculoskeletal disorders causing abnormal force on normal joint or normal force on abnormal joint (Henrotin *et al.,* 2005; Johnston, 1997). Examples are stress on joints due to obesity or excessive exercise (Elliot *et al.,* 2007).

Osteoarthritis occurs in all age groups but older dogs are predisposed and an estimated twenty percent of all dogs over 1 year of age, are affected (Pfizer Animal Health, 1996). Few epidemiological studies have been carried out on osteoarthritis in dogs in comparison to humans and the prevalence in different species remains unknown (Henrotin *et al.,* 2005). However Elliot *et al.* (2007) stated that 45% of the large breed dogs, such as German Shepherd and Labrador Retriever, have osteoarthritis and are generally are more susceptible due to being genetically predisposed. Large breed dogs also seem to have a higher rate of orthopaedic diseases eventually progressing into osteoarthritis.

Goldring & Goldring (2007) have investigated the source of pain in osteoarthritis and considered the synovial products formed during inflammation as potential contributors to symptoms of pain. Painful stimuli include neuropeptides such as substance P and damaged synovial cells releasing pro-inflammatory cytokines and producing prostanoids (Goldring & Goldring, 2007; Elliot *et al.,* 2007). These are detected by afferent sensory nerves, nociceptors, which can be found in the joint capsule, ligaments, periosteum and subchondral bone. When the limits of physiological articulation are exceeded, the action potentials increase considerably and the central nervous system detects this as pain (Goldring & Goldring, 2007).

Anti-inflammatory and analgesic drugs

NSAIDs

Ever since the first Nonsteroidal anti-inflammatory drug (NSAID) aspirin was marketed in 1899, NSAIDs have been used to treat chronic pain and are commonly used to treat osteoarthritis in dogs. Their rapid efficacy when it comes to alleviating pain are making them popular although they are associated with, at times, serious adverse effects (Innes *et al.,* 2010a).

Mechanism of action

The group of drugs aim to inhibit the cyclooxygenase (COX) enzyme which catalyses the conversion of arachidonic acid in the prostaglandin- and thromboxane synthesis (Innes *et al.,* 2010b*)*. By doing that, the so called COX-inhibitors, achieve anti-inflammatory, antipyretic and analgesic characteristics. The anti-inflammatory and analgesic ability of NSAIDs are most likely derived mainly from the inhibition of prostaglandin E_2, (PGE_2), whose concentrations have shown elevated in synovial fluid from osteoarthritic joints (Innes *et al.,* 2010a). Both PGE_2 and prostacyclin I_2 (PGI_2), possess pro-inflammatory characteristics dilating arterioles and mediating pain perception through histamine and bradykinin. PGE_2 further sensitize central and peripheral nociceptors (Bergh & Budsberg, 2005).

The COX enzyme can it its turn be subdivided into two isoforms, cyclooxygenase-1 (COX-1) and -2 (COX-2). They are catalysing synthesis of different prostanoids having numerous of physiological effects. The most important being summarized in Table 1.

TABLE 1: ***Showing the prostanoids synthetized in the COX-pathways and their effects***

COX-1	Prostaglandin E_2 (PGE_2)	-Vasodilation, -Sensitization of both central and peripheral nociceptors, -Numerous of gastrointestinal effects protecting the stomach, -Increase sodium and water excretion and change chloride transport in the kidneys. -Stimulate renin secretion altering renal blood flow in dogs
	Thromboxane A_2 (TXA_2)	-Increased platelet clumping
COX-2	Prostaglandin E_2 (PGE_2)	-*See COX-1*
	Prostacyclin (PGI_2)	-Vasodilation, - Decreased platelet clumping -Similar gastro protective effects as PGE_2 -Similar renal effects as PGE_2

(Simmons, 2004; Osborn et al., 1984)

To distinguish COX-1 and COX-2 one could say that COX-1 is expressed in almost all tissues for the maintenance of normal physiological functions. The number of COX-2 however, tends to increase during inflammation under influence of pro-inflammatory cytokines. The level of COX-2, for example, increases in endothelial cells, chondrocytes, synovial cells, osteoblasts and macrophages during osteoarthritis. Although this division may appear distinct, the complete correlation between the two COX isoforms, is much more complex (Innes *et al.*, 2010a). COX-2 is for example, constantly present in the kidney, gastrointestinal tract, neural- and reproductive system, necessary for normal function of the tissues (Lomas & Grauer, 2015).

The distinction between "good" and "bad" is thus subtle when it comes to COX inhibition. The general belief today is that NSAIDs who selectively inhibit only COX-2, generate analgesia with less adverse events, especially concerning the gastrointestinal tract, than those of COX-1 inhibition. These drugs, allowing continued PGE_2 protective production through COX-1, are called cyclogenase-2 inhibitors (COXIBs) (Innes *et al.*, 2010a; KuKanich *et al.*, 2012).

Adverse effects NSAIDs

The number of adverse drug effects associated with NSAIDs is higher than for any other drug used for pets (The Federal Drug Administration Centre for Veterinary Medicine, 2008). Therefore, it is of vital importance to understand the NSAIDs´ mechanisms of action. COX-1 and -2 inhibition possess different therapeutic possibilities since they, to various degrees, negatively affect organs. The most common being the gastrointestinal tract, the kidneys, the liver and cardiovascular system (KuKanich *et al.*, 2012). The two most common will be addressed in this thesis.

Gastrointestinal tract

The most talked about adverse effects regards the gastrointestinal tract where both COX-1 and COX-2 are normally expressed in dogs. PGE_2 and PGI_2 both help protect the organ, increasing blood flow and mucus- and bicarbonate production at the same time as they slow down acid secretion. Hence inhibition of these enzymes or direct irritation of the mucosa after administration of the drug, can lead to injuries causing gastritis, enteritis, ulceration and perforation. Showing clinical signs as diarrhoea and/or vomiting (KuKanich *et al.*, 2012).

A clinical trial on rats showed that inhibition of both COX-1 and COX-2, putting a stop to all the protective factors of especially PGE_2, is needed in order to induce NSAIDs related gastric injury (Wallace *et al.,* 2000). This indicates that COXIBs would be related with less gastrointestinal adverse effects, however according to Innes *et al.* (2010a), it hasn't yet been scientifically proven in veterinary medicine.

Kidneys

The kidney is the organ receiving the second highest reports of adverse events associated with use of NSAID's. Furthermore, no NSAID has proven safe for the kidney. The decreased prostanoids synthesis (especially the one of PGE_2) followed by NSAIDs usage, shows in the kidney as decreased RBF (volume of blood delivered to the kidney per unit of time) and/or GFR (volume of fluid filtered by the kidneys per unit of time). The decreased excretion of sodium and water increase the risk for oedema and hypertension and in the event of severe cases, NSAID usage could lead to acute kidney injury (AKI) (Lomas & Grauer, 2015).

Both COX-1 and COX-2 are expressed in the renal of dogs, however Radi (2009) presented information showing significant interspecies differences in distribution and presence of the two. Basal levels of COX-2 is significantly higher in dogs than other species such as humans and monkeys. A study was carried out by Sellers *et al.* (2005) where dogs and monkeys were given a nonspecific COX-inhibitor for two to six weeks to compare the differences in COX-expression between the two. The study showed that although the reduction in renal prostaglandin levels were similar between the two groups, a higher level of renal toxicity showed by decreased urine output and sodium excretion, was present amongst the dogs. This probably due to greater inhibition of COX-2 in the dogs hence possibly making them more sensitive to COXIBs.

Hypersensitivity and behavioural changes

Different species have demonstrated COX-1 versus COX-2 sensitivity to varying extents and the relative safety of one NSAIDs for a species cannot be automatically be translated as safe to another (Innes *et al.,* 2010a). According to the package insert for dogs Loxicom® (Norbrook Laboratories Limited), there is an individual hypersensitivity which must be assessed case by case and in addition to the direct adverse effects, individuals can exhibit behavioural changes such as lethargy and depression.

Drug-drug interactions and long-term treatment

As mentioned before, NSAIDs can cause kidney disease and concurrent treatment with other nephrotoxic drugs, such as aminoglycosides, is a risk factor. NSAIDs also have effect in the treatment of hypertension, lowering the effect of ACE-inhibitors and beta blockers in humans. Furthermore a treatment containing both NSAIDs and corticosteroids increases the risk of gastrointestinal- and nephrotoxic injuries and has negative impact on platelet function in dogs (KuKanich *et al.*, 2012).

Concurrent treatment with different NSAIDs increases the risk of especially gastrointestinal damage and therefor a washout period is recommended if changing from one NSAID to another (KuKanich *et al.*, 2012).

Recommendations regarding treatment of osteoarthritis using NSAIDs varies from intermittent to continuous, so called long-term treatment, depending on the author. The potential risks of long-term treatment include dogs developing drug tolerance over time and an increased incidence of adverse effects associated with NSAIDs (Innes *et al.,* 2010a).

Innes *et al.* (2010a) further believe it is most likely the perception of the risk of adverse events that restricts NSAIDs long time use. There are no exact and controlled estimates for the incidence of adverse events with long-term use in large numbers of dogs (Innes *et al.,* 2010a; Innes *et al.,* 2010b). Lomas and Grauer (2015) share the view that NSAIDs are often used for chronic management of osteoarthritis, although few long-term safety studies exist.

A chronic use of NSAIDs is unfavourable to dogs with concurrent disease such as liver- and renal disease, heart failure, volume depletion, hypotension and sodium depletion *(*KuKanich *et al.,* 2012). This complicates and create restrictions on treatment, especially in older dogs who tend to suffer from more illnesses over time. One example is chronic kidney disease (CKD) that, just as osteoarthritis, increases with age. This makes it likely to believe that many dogs will have an early stage CKD as being treated with NSAIDs for osteoarthritis. As CKD can decrease renal perfusion when nephrons are lost, the kidney becomes more dependent on COX-2 production of prostanoids to remain fluid balance and RBF (Lomas & Grauer, 2015).

Disease-modifying osteoarthritis agents

In order to move forward with the medical treatment of osteoarthritis in dogs, research has been developing alternative treatment methods. Disease modifying osteoarthritis agents focus on slowing down the progression of cartilage degradation and promote cartilage matrix synthesis. Despite poorly satisfying scientific studies validating their efficacy, the so called slow-acting disease modifying osteoarthritis agents, are frequently used today. They can further be divided into parenterally products and orally administered products (McLaughlin, 2000).

Glucosamine- and chondroitin sulphate

Henrotin *et al.* (2005) presented glucosamine- and chondroitin sulphate as the main examples of nutraceuticals in the management of canine osteoarthritis. Stating they have improved symptomatic as well as structural characteristics of osteoarthritis in both animals and humans. However this is a well-debated topic facing many opponents with sceptical attitude towards its efficiency in dogs (Moreau *et al.,* 2003)**.** Furthermore no scientific trials have been carried out to demonstrate the disease modifying properties on dogs (Henrotin *et al.,* 2005).

Mechanism of action

The cartilage matrix (ECM) is divided into collagen, proteoglycans and water, and disturbances in distribution between these, play part in changes typically associated with osteoarthritis (Johnston, 1997).

Proteoglycans constitute the biggest part of the ECM and is made up of a core protein to which several types of glycosaminoglycan (GAG) chains are attached (Johnston, 1997). Glucosamine (GS) is an amino-monosaccharide and a precursor in the GAG-synthesis in the ECM and synovial fluid (Elliot *et al.*, 2007). Dogs have shown to absorb 87% of the GS administered in the gastrointestinal tract and by synthetically adding GS, core proteins are said to be activated

and the proteoglycan synthesis is stimulated in order to achieve structure modifying properties. (Elliot *et al.,* 2007; Setnikar *et al.,* 1986). A study made in vitro by Bassleer *et al.* (1998) showed that GS and chondroitin sulphate (CS) increased the production of proteoglycans in human articular chondrocytes.

Chondroitin sulphate (CS) in turn is one of the most common GAG in articular cartilage (Johnston, 1997). These are said to operate by providing additional substrate for proteoglycan synthesis (Elliot *et al.,* 2007)

Few studies have been carried out on dogs but in a human *in vitro* study, Largo *et al.* (2003) investigated the possibility that GS also possess anti-inflammatory hence pain relieving abilities. The study showed amongst other, that GS inhibit PGE_2 synthesis through inhibition of IL-1 induced COX-2. The scientific knowledge regarding the mechanism of action of these nutraceuticals is however yet to be fully discovered (Largo *et al.,* 2003).

Adverse events

The safety profile for GS has been estimated as excellent over time. In a systemic review by Anderson *et al.* (2005), more than seventeen studies on animals including rats, mice, rabbits, dogs and horses, were evaluated based on acute-, sub-chronic- and chronic toxicity. The studies ranged from twelve to three hundred and sixty-five days. It was concluded that oral GS appears to be well tolerated by rats, mice, rabbits, dogs and horses. Although Henrotin *et al.* (2005) have reported some, on the rare occurrence, adverse effects from a human systemic review. Seven out of one thousand and eighty-six patents randomized to GS had to be withdrawn from the study due to GS-related toxicity and forty-eight reported GS-related adverse effects. They predominantly regarded the gastrointestinal tract and went away as the patient went of GS.

Efficacy NSAIDs vs glucosamine- and chondroitin sulphate

In a study conducted by Moreau *et al.* (2003) the effects of two different NSAIDs (carprofen and meloxicam) were compared with a combined treatment of glucosamine, chondroitin sulphate and manganese ascorbate for sixty days. A total of seventy-one dogs with osteoarthritis participated and they were divided into four groups, the fourth being a placebo group. The results were measured by an objective gait analysis and a subjective observation carried out by the owners and the orthopaedic surgeons. Dogs treated with NSAIDs showed significant improvements objectively and subjectively while dogs treated with nutraceuticals, did not show any improvements. However, a dog treated with carprofen showed adverse effects in form of hepatopathy at the end of the study. Furthermore, two dogs in the NSAIDs treatment group had to withdraw before the end of the study due to adverse effects. One showing clinical signs of vomiting and the other being diagnosed with toxic idiosyncratic hepatitis to carprofen.

In another study carried out by McCarthy *et al.* (2007), forty-two dogs with confirmed osteoarthritis were divided into two treatment groups; glucosamine- and chondroitin sulphate (Glu/Cs) and a positive control group (carprofen). After seventy days of treatment, thirty-five dogs remained (two had to withdraw due to adverse effects, both from the Glu/Cs treatment group). The result, based on subjective evaluation by participating veterinarians, showed statistically significant improvements in scores for pain, weight bearing and severity of illness

in the Glu/Cs treatment group. However dogs treated with carprofen showed the same improvement on day forty-two of treatment.

The two studies above present disagreeing results. One explanation could be that glucosamine- and chondroitin sulphate need more than sixty days to reach full efficiency and that the first trial might have administered a dose that was too low. Furthermore, the second study does not elaborate what side effects were seen in the two dogs being withdrawn from the study, making it harder to draw conclusions. Also, the second study did not have an objective measurement analysis possibly affecting the study result.

Weight management in dogs with osteoarthritis

Elliot *et al.* (2007) suggested that adjustments to achieve appropriate lifestyle, including weight reduction and suitable physical exercise, might be the most important aspect of therapy when it comes to clinically improve osteoarthritis. In this thesis, the importance of weight management will be addressed.

Excess body weight contributes to increased mechanical stress on the joints, which is a risk factor for the development of osteoarthritis. In addition it is a contributing factor to increased stress on already tender joint, something that accelerate the disease progression (Elliot *et al.*, 2007; Rychel, 2010). Marshall *et al.* (2009) presented numbers from studies investigating the estimated prevalence of canine obesity to be 24% in 1986 and 41% in 2005, showing an increasing trend amongst domesticated dogs.

Marshall *et al.* (2009) further developed that the relationship between obesity and osteoarthritis seem to involve both biomechanical and biochemical factors. Adipose tissue is said to have a role in biological processes mediated by the produced peptide hormone leptin. Leptin is said, amongst other, to inhibit the effect on long-term growth of cultured chondrocytes by inducing matrix metalloproteinases (MMPs) in dose-dependent manner and induce IL-1.

A study carried out by Smith *et al.* (2006) evaluated the effect of lifelong food restriction and the development of radiographic evidence of osteoarthritis in hip joints in Labrador Retrievers. The study contained forty-eight dogs divided into two groups being control fed respectively restrictedly fed (which was 25% less) over fourteen years. The study showed that dogs in the restricted group had delayed or prevented development of radiographic osteoarthritis. The radiologist who scored the radiographs was not aware of which group the dog was part of. However the differences in exercise between the dogs were not controlled and the parents to the dogs were chosen by subjective criteria.

Ethical aspect of osteoarthritic treatment in dogs

According to the Swedish Medical Products Agency (2005), ”All chronic pain where the connection with incurable conditions where pain cannot be treated satisfactorily, ethical and animal welfare aspects must be taken into account and euthanasia in such cases should be considered in consultation with the animal's owner.”

Today many dogs with osteoarthritis are treated but it is questionable if it is always ethically defensible. According to The Swedish Animal Welfare Act (SFS 1988:534), the animals are to be treated well and to be protected from unnecessary suffering continuing to be managed in

such a way that it promotes their health and allows them to behave naturally. The dog has a natural need for movement which is prevented to different degrees in osteoarthritis. Is it ethically defensible to continue treating dogs who can no longer perform their natural behaviour, along with being exposed to pain where analgesics might be inadequate and where to draw the line?

DISCUSSION

Osteoarthritis is a complex condition associated with different degrees of pain and NSAIDs is the most common therapeutic treatment method today (Simmons, 2004). NSAIDs is thus to question because of its, in some cases, serious adverse effects.

Although COXIBs are said to give less gastrointestinal adverse effects in dogs there are no published reports saying that these would also be associated with fewer adverse effects on the kidneys and liver (KuKanich *et al.,* 2012). There are even indications that COXIBs could contribute to increased risk of renal toxicity in dogs though they seem to have more COX-2 naturally expressed in parts of the kidneys (Sellers *et al.,* 2005).

There is also an existing uncertainty regarding the safety profile over time in dogs. There are few long-term studies on NSAID therapy and different therapists tend to give different treatment advice (Innes *et al.,* 2010a). More research on the long-term effects of NSAIDs in dogs and furthermore research is also needed on COXIBs to see how toxic they are for the liver and kidneys.

The prevalence of osteoarthritis increases with age, and this is a problem in older dogs because they also have an increased risk of other diseases. Dogs with other diseases related to the areas where NSAIDs related adverse effects are shown, are warned against treatment (KuKanich *et al.,* 2012*).* This and the fact that concurrent treatment with corticosteroids, nephrotoxic drugs or other NSAIDs is associated with risks, might make it impossible to treat osteoarthritis with NSAIDs in some dogs.

So there are several arguments for being sceptical to NSAIDs in the treatment of osteoarthritis in dogs. Another is whether or not treatment of only the pain is inadequate. Some argue that analgesic effect from NSAIDs potentially open up to the ability of increased physical mobility (Innes *et al.,* 2010b). If that being true, it would be arguable that NSAIDs could contribute to secondary improved condition due to increased muscle mass around the joint (Innes *et al.,* 2010b). Another way of mediating joint repair is by stimulating ECM synthesis and thus relieve the pain in the long term, something that glucosamine- and chondroitin sulphate aim to do.

Although glucosamine- and chondroitin sulphate are the most common nutraceuticals in the treatment of osteoarthritis in dogs, few scientific studies prove their efficacy. We need more research carried out on the dog to be able to draw conclusions about the disease modifying effects and further if their analgesic ability is adequate. In the studies being compared in this thesis, glucosamine- and chondroitin sulphate take longer time to reach analgesic effect and appear to have a generally poorer analgesic capacity compared with NSAIDs.

Most likely there is no easy solution to the treatment of osteoarthritis. Johnston *et al.* (2008) said: "Because of the complex neurobiology of pain, it is reasonable to believe that multimodal pharmacologic and non-pharmacologic therapy is advantageous for the treatment of osteoarthritis." This statement makes a lot of sense in that different treatment methods seem to play different roles in the prevention of development as well as progression of osteoarthritis. Physical rehabilitation and weight management seem to have major impact mediating both.

As the treatment situation is today, it seems analgesia using NSAIDs is necessary from an ethical and animal welfare point of view. This as other treatment methods haven't scientifically proven to reach the same analgesic effect. However, it is important to think about how far to go in the treatment of dogs with osteoarthritis and how much pain should be allowed. There is a risk that dog owners adapt a progressive mental tolerance regarding their dog's condition. They might stop objectively comparing the state of their sick dog with the state of healthy dogs and settle with the degree of improvement that can be achieved with current treatments on the market. This, despite it possibly being nonsufficient from an ethical- and animal welfare perspective.

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