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NUTRACEUTICAL TREATMENT IN DOGS AND CATS

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Chondroprotectants and nutraceuticals have become an attractive adjunctive or alternative treatment for cats and dogs suffering from osteoarthritis. Chondroprotectants are available as oral nutraceuticals oral and injectable pharmaceuticals. At the present time, recommendations cannot be made as to which chondroprotectant is best for each dog and cat afflicted with osteoarthritis. Head to head comparisons of these products have not been made. In addition, it is not known when the different mediators of osteoarthritis play an important role. The possibility exists that mediators of pain and degradation (prostaglandins, free radicals, metalloproteinases, serine proteases, etc) may change during the course of disease. It would be ideal to know what the predominant mediators were in an individual suffering from osteoarthritis in order to accurately select the best product to treat that individual patient. At the present time, the best recommendation is to use products having well-designed experimental and clinical research evaluating efficacy and safety, as well as products that are manufactured under the high quality standards practiced by the pharmaceutical industry.

CHONDROPROTECTANTS AND NUTRACEUTICALS – MECHANISM OF ACTION

The mechanism of action of many of these products is unknown or unproven. Other products, on the other hand, have been substantiated with experimental and clinical trials. Dietary supplements and nutraceuticals cannot be sold under the premise as a treatment for a medical condition. These products cannot be marketed with the intent to diagnose, treat, cure or prevent disease. Instead, they must be marketed as nutrients necessary for supporting or improving normal structure and function of the joint. Chondroprotective agents presumably influence cartilage metabolism by providing substrate and upregulating chondrocytes. They also appear to inhibit degradative enzymes including the metalloproteinases, serine proteases, and free radicals. Lastly, some of these products inhibit the formation of microthrombi in the periarticular vasculature, thus supporting a normal blood supply to the joint tissues.

PATHOPHYSIOLOGY OF OSTEOARTHRITIS

Osteoarthritis is characterized by a low-grade inflammatory process that leads to progressive changes in the structure and function of the joint. Joint capsular thickening and inflammation leads to pain, decreased range of motion and decreased function. Synovial fluid alterations cause pain, a change in joint biomechanics, and a reduction in the protective mechanisms of the joint. Loss of articular cartilage leads to pain, loss of function and establishes a mechanism for perpetuating low-grade inflammation and progressive OA. Increased density of the subchondral bone indirectly affects the joint by increasing the amount of force placed on the articular cartilage. Osteoarthritis is characterized by changes in the structural components of articular cartilage. The initial change involves the loss of proteoglycans from the extracellular matrix due to increased destruction and decreased production. The breakdown and loss of collagen and chondrocytes occur as disease progresses, leading to irreversible change.

TREATMENT OF OSTEOARTHRITIS

Treatment may include surgery, weight loss, exercise modification, physical therapy, pharmacological therapy and chondroprotective therapy. In cases of secondary OA, the underlying cause must be identified and eliminated to minimize the progression and long-term effects of osteoarthritis. Nonsteroidal anti-inflammatory drugs (NSAID) should be considered because of their ability to reduce pain and reduce prostaglandin production. Chondroprotective agents include oral nutraceuticals and injectable glycosaminoglycans. These products may inhibit mediators of inflammation and stimulate metabolic activity of synoviocytes and chondrocytes.

Glucosamine Hydrochloride / Chondroitin Sulfate / Manganese Ascorbate

The combination of glucosamine hydrochloride, chondroitin sulfate and manganese ascorbate (GCM) is a commonly used nutraceutical in osteoarthritic companion animals. Cosequin® (Nutramax Laboratories, Baltimore, MD) is marketed as a glycosaminoglycan enhancer, capable of providing raw materials needed for the synthesis of endogenous synovial fluid and extracellular matrix of cartilage. Cosequin contains glucosamine, which has been described as the building block of the matrix of articular cartilage. It has been described as a preferential substrate and stimulant of proteoglycan biosynthesis, including hyaluronic acid and chondroitin sulfate. Cosequin also contains chondroitin sulfate, mixed glycosaminoglycans, and manganese ascorbate for the purpose of promoting glycosaminoglycan production. Chondroitin sulfate appears to inhibit degradative enzymes associated with osteoarthritis including metalloproteases and collagenases. These degradative enzymes breakdown the cartilage and hyaluronan in synovial fluid. The combined action of glucosamine and chondroitin sulfate is synergistic. Manganese is a cofactor in the synthesis of GAGs and its supplementation may aid in cartilage matrix synthesis. Manganese is also necessary for the synthesis of synovial fluid. It is possible that manganese may have anti-oxidant properties as well. Overdose safety studies have been conducted with Cosequin in the dog, cat and horse. No persistent abnormality in hematology, serum chemistry or hemostatic parameters were observed in these studies.No known side effects of clinical significance have been seen in the cat or dog.

Clinical and experimental studies support the use of GCM in combination or as individual components. Leeb, et al. performed a meta-analysis of the clinical efficacy of chondroitin sulfate in humans. A total of 16 published studies were examined, with 7 trials of 372 patients selected for the meta-analysis. All selected studies were randomized, double blinded designs in parallel groups, however rescue medication (analgesics or NSAIDs) were permitted, typical of human clinical studies of OA. Chondroitin sulfate was shown to be significantly superior to placebo with respect to the Lequesne index (a validated, subjective assessment of pain associated with OA). Patients showed at least a 50% improvement in study variables in the chondroitin sulfate group compared to placebo.A double-blind clinical study in horses showed Cosequin's efficacy for treatment of DJD associated with navicular disease. Administration of Cosequin to dogs with experimentally-induced OA via transection of the cranial cruciate ligament showed increased concentration of OA markers, indicative of cartilage matrix synthesis. Glucosamine, chondroitin sulfate and manganese ascorbate may act as

signaling molecules for up-regulation of the genes for aggrecan and collagen II, not just as substrates for cartilage production. Cosequin has also been found to suppress the inflammatory affects of chemically-induced acute synovitis and experimental immune-mediated arthritis.

The fate of orally administered chondroitin sulfate appears to be affected by the molecular weight of the molecule. Low molecular weight (LMW) chondroitin sulfate is absorbed in approximately 2 hours and accumulates in the serum over time, having an estimated bioavailability of 200%. Glucosamine hydrochloride also is absorbed in less than 2 hours, but does not accumulate over time. Orally administered glucosamine has been found to be readily absorbed and reaches highest concentrations in articular cartilage.

Mixed Glycosaminoglycan Products

Many other oral glycosaminoglycan or glucosamine products are available either as single or multiple ingredient products. Most of the glycosaminoglycan products contain chondroitin sulfate or "mixed" glycosaminoglycans. Different glucosamine salts are available. Much controversy exists regarding the necessary purity, concentration and type of glycosaminoglycan or glucosamine product necessary to provide beneficial effects to cartilage.

The New Zealand green lipped mussel (GLM, *Perna canaliculus*) is known to contain glycosaminoglycans, omega-3 fatty acids, amino acids, vitamins, and minerals. This product is available as a sole dietary supplement or as an additive in canine diets. *Perna canaliculus* is purported to have mild anti-inflammatory and chondroprotective actions, but these effects remain to be unequivocally substantiated in humans and animals. Beneficial effects have been purported in one study in humans suffering from Rheumatoid arthritis and osteoarthritis. () A recent study in dogs found improvement in joint pain and swelling in arthritic dogs fed a complete diet containing 0.3% GLM. No effect was seen on joint crepitus, range of motion or mobility scores. Although the study concludes that a GLM supplemented diet can alleviate symptoms of arthritis in dogs, several points may be questioned in the study. The dogs used in the study were not definitively diagnosed as having osteoarthritis. Joint swelling, which is not a consistent finding in osteoarthritic joints, was significantly improved. However, joint mobility, range of motion and crepitus, commonly associated with osteoarthritis, showed no improvement. Additionally, control dogs showed a marked worsening in joint pain and swelling over the 6 week period of the study, which is inconsistent with dogs, selected for a chronic, slowly progressive condition such as osteoarthritis. This study also included a subjective scoring system, with parameters added across joints for a total score within the animal. It is difficult to envision that certain scores, such as the measurement of joint swelling of the hip and shoulder, could be accurately or consistently obtained. The validity of the scoring system can be questioned. Further study is warranted prior to unequivocal acceptance of this substance as a chondroprotective agent or nutraceutical useful in osteoarthritic dogs.

Glucosamine

Glucosamine salt supplements are most commonly found as glucosamine hydrochloride or glucosamine sulfate. Both forms are readily available, however the hydrochloride form provides more glucosamine per unit weight than the sulfate form. Another form, N-acetyl glucosamine, appears to have less activity than the hydrochloride and sulfate forms. Glucosamine is commonly found in combination products containing other products including chondroitin sulfate and manganese ascorbate. Glucosamine is an amino sugar that is a precursor to glycosaminoglycans present in the extracellular matrix of articular cartilage. Normal chondrocytes have the ability to synthesize glucosamine. Osteoarthritic cartilage, however, appears to have a decreased ability to synthesize glucosamine. Exogenous glucosamine stimulates the production of proteoglycans and collagen by chondrocytes in cell culture. Glucosamine has good bioavailability when administered orally or parenterally, having good distribution to all body tissues and reaching highest concentrations in the liver, kidney and articular cartilage. Oral glucosamine was shown to have an intestinal absorption rate of 87%. Orally administered glucosamine sulfate has been associated with relief of clinical signs of DJD and chondroprotection in clinical and experimental studies in man. Although glucosamine has a slower onset of relief of clinical signs associated with DJD as compared to ibuprofen, two clinical trials in man found it to have equal long-term efficacy. Oral glucosamine was found to improve clinical performance in humans with osteoarthritis. Use of this product as an individual agent in animals has been proposed, but adequately controlled clinical studies have not been performed to substantiate its efficacy. Glucosamine is becoming a popular supplement to pet foods for osteoarthritic pets.

Chondroitin Sulfate

Chondroitin sulfate is a predominant glycosaminoglycan found within the extracellular matrix of articular cartilage. Oral supplementation of exogenous chondroitin sulfate has been advocated anecdotally for many years as a treatment for osteoarthritis in humans and animals. This compound is often found in combination with other nutraceuticals such as glucosamine and free radical scavengers. Chondroitin sulfate (CS) has been found to decrease interleukin-1 production, block complement activation, inhibit metalloproteinases, inhibit histamine-mediated inflammation, and stimulate glycosaminoglycan and collagen synthesis. Oral absorption of chondroitin sulfate has been reported using a variety of techniques. Some controversy exists as to the fate of CS following oral administration. Various methods have been used to show CS has the ability to be intestinally absorbed, but uncertainty remains as to whether the majority of CS is absorbed intact or as a subunit of CS. A highly pure, low molecular weight form of CS has been found to have good absorption and bioavailability. Clinical studies have shown improvement in clinical signs associated with osteoarthritis in human patients receiving CS supplementation.

Free Radical Scavengers

Another class of nutraceutical that has been promoted to reduce inflammation is the free radical scavengers such as superoxide dismutase (SOD), bioflavonoids, glutathione and DMSO. Oxygen-derived free radicals (superoxide, hydrogen peroxide, hydroxyl radical) are thought to play a role in the progression of DJD through their ability to damage cells by oxidative injury. Oxidative injury leads to depolymerization of hyaluronic acid, destruction of collagen and decreased production of proteoglycans. Superoxide dismutase and glutathione are endogenous antioxidants present in mammalian cells that inhibit production of oxygen free radicals. This enzyme acts to stabilize phagocyte cell membranes and lysosomes, and reduce superoxide radical levels in tissues, with a resultant decrease in free radical generation.The efficacy, bioavailability and safety of many oral antioxidants are unknown. In addition, this product may have potential

manufacturing or storage problems, which may lead to less active ingredient being available to the pet than is labeled on the product. A recent study found discrepancies in certificate of analysis and labeled contents in six SOD products. Since this study, several new products have become available which may have resolved this problem.

DMSO, which is used as a topical agent when treating musculoskeletal problems, has the ability to penetrate most tissues, including skin. (40) Topical application of 20 ml/day of a medical grade DMSO(70-90 % solution) every 6 to 8 hours for up to 14 days has been recommended to treat local inflammation. Side effects with topical use are minimal, but include a garlic odor to the breath.

Superoxide dismutase is an endogenous antioxidant present in mammalian cells that inhibits production of oxygen free radicals. This enzyme acts to stabilize phagocyte cell membranes and lysosomes, and reduce superoxide radical levels in tissues, with a resultant decrease in free radical generation. The efficacy of exogenous superoxide dismutase is unknown. One author recommends giving 5 mg subcutaneously for 6 days in the dog, followed by alternate day therapy for 8 days. The manufacturer recommends giving 2.5 mg/kg subcutaneously five times a week for two weeks for treatment of spondylitis or disc disease.

Bioflavanols are also purported to have strong antioxidant properties. Grape seed meal has a rich source of bioflavanols. Bioflavonols are purported to scavenge free-radicals, alleviate inflammation induced by oxidative damage and inhibit degradative enzymes released b oxidative cells. One double-blind, randomized study in dogs found improvement in clinical signs attributable to hip osteoarthritis in dogs supplemented with a product containing bioflavonoids, SOD and glutathione. Other clinical studies also report improvement in function and decreased pain in osteoarthritic dogs and horses. These studies also report improvement after 2-3 weeks of product administration. Bioflavanols are available commercially usually in combination with glucosamine and hydrolyzed collagen or with an assortment of other antioxidants, including selenium, vitamin E and superoxide dismutase.

Methyl-Sulfonyl-Methane (MSM)

MSM has been suggested as an agent for management of pain, inflammation and as an antioxidant. The rationale behind its use, according to the manufacturer and others, is the possibility of a dietary sulfur deficiency. Methyl-sulfonyl-methane (MSM) is a white, crystalline, water soluble, odorless and tasteless compound that is sold as a supplement. It is actually a metabolite of industrial-grade dimethylsulfoxide (DMSO). Methylsulfonylmethane is found naturally in certain foods; however, it is destroyed during processing. DMSO is a byproduct of the wood pulp processing industry and is also available in a medical grade, which is approved only for the treatment of interstitial cystitis in the U.S. Radiolabelled sulfur from MSM has been found in amino acids (methionine and cysteine) of proteins in guinea pigs following experimental oral administration. There are no controlled experimental or clinical studies available to support the use of MSM for management of OA in dogs. Companies supplying MSM base their claims of relief of pain and inflammation on results of studies conducted with DMSO. Little is known about safety of the product. Sold in capsules for human use, MSM is available in powder form, tablets and capsules for use in horses and small animals. Manufacturer recommendations for dosage should be followed. Its use cannot be recommended at this time, however, due to the above-mentioned lack of studies and knowledge about safety.

Omega-3 Fatty Acids

Omega-3 fatty acids have recently gained popularity for their potential use in pets with DJD. These products are available naturally, as supplements in pet foods and as nutraceutical supplements. Omega-3 fatty acids are desaturated in the body to produce eicosapentaenoic acid, which is an analog of arachidonic acid. Prostaglandins, thromboxanes and leukotrienes are produced from both of these compounds through the action of cyclooxygenase and lipoxygenase. The products resulting from arachidonic acid metabolism are proinflammatory, proaggregatory and immunosuppressive as compared to the metabolic by-products of eicosapentaenoic acid which are less inflammatory, vasodilatory, antiaggregatory and not immunosuppressive. The use of omega-3 fatty acids could theoretically benefit dogs and cats suffering from DJD by decreasing inflammation and reducing the occurrence of microthrombi; however, objective data is lacking to attest to this products efficacy. The ideal ratio of N6:N3 fatty acids for canine diets is controversial, but a current recommendation is between 10:1 and 5:1. A recent study reported lower PGE_2, reduced clinical and radiographic signs of osteoarthritis in experimental dogs undergoing cranial cruciate ligament transection while being fed a diet low in N6 fatty acids.

Polysulfated Glycosaminoglycan

Adequan®[a]) (Luitpold Pharmaceuticals, Shirley, NY) is a drug that is gaining popularity for use in dogs is a glycosaminoglycan polysulfate ester (GAGPS). It is purported to be both chondroprotective and chondrostimulatory. Chondroprotection is achieved due to the inhibition of various destructive enzymes and prostaglandins associated with synovitis and DJD. GAGPS has been found to inhibit neutral metalloproteinases (stromelysin, collagenase, elastase), serine proteases, hyaluronidase, and a variety of lysosomal enzymes. The drug has also been found to inhibit PGE_2 synthesis, generation of oxygen-derived free radicals and the complement cascade. Protection of articular cartilage has also been seen on gross and histological examination in numerous experimental studies. GAGPS has been found to stimulate anabolic activity in synoviocytes and chondrocytes. Chondrostimulatory effects are characterized by increased synoviocyte secretion of hyaluronate and enhanced proteoglycan, hyaluronate and collagen production by articular chondrocytes. GAGPS also has anticoagulant and fibrinolytic properties that facilitate clearing of thrombotic emboli deposited in the subchondral and synovial blood vessels. While the majority of experimental and clinical studies support the premise that GAGPS possesses properties of chondroprotection and chondrostimulation, some studies have found GAGPS to have either no beneficial effect or to actually have a detrimental effect on cartilage metabolism.

A clinical study in hip dysplastic dogs found the greatest improvement in orthopedic scores at a dose of 4.4 mg/kg (2 mg/lb) given intramuscularly every 3 to 5 days for 8 injections. Use in cats has also been reported at the same dose. Another study found twice weekly intramuscular administration of 5.0 mg/kg GAGPS from 6 weeks to 8 months of age in growing pups that were susceptible to hip dysplasia resulted in less coxofemoral subluxation. The longevity of relief provided by GAGPS is unknown. Most studies have evaluated its effect in

the short term only. Anecdotal reports of duration of amelioration of clinical signs range from days to months. It is also not known whether the complete series of injections are needed once clinical signs return or whether a shorter regimen would suffice.

Side effects of GAGPS in dogs include short-term inhibition of the intrinsic coagulation cascade as well as inhibition of platelet aggregation when given 5 mg/kg or 25 mg/kg intramuscularly. Also, GAGPS has been found to inhibit neutrophils and complement which may predispose to infections, especially when injected intraarticularly under contaminated conditions. GAGPS has been reported to cause sensitization reactions in man, but this has not been reported in the dog.

Pentosan polysulphate (Cartrophen-Vet®[b], Biopharm Australia, Sydney, Australia is a polysaccharide sulfate ester (mean molecular weight of 6,000 daltons) prepared semi-synthetically from beech hemicellulose. The drug is approved for use in dogs and horses in Australia and is used in a similar manner as Adequan for relieving clinical symptoms of DJD. Pentosan polysulphate can be administered intraarticularly, intramuscularly, subcutaneously or orally. The recommended dose for intraarticular use is 5-10 mg per joint weekly, as necessary. The intramuscular or subcutaneous dose in dogs is 3 mg/kg, once weekly for 4 weeks. This regimen can be repeated as necessary. A double-blind study evaluating the efficacy of this product for treatment of DJD in the dog found this dose to be ideal. This dose has also been used anecdotally in cats. Oral calcium pentosan polysulphate given at a dose of 10 mg/kg weekly for 4 weeks, then repeated every 3 months, was found to reduce the presence of cartilage break-down products in osteoarthritic cartilage.

Sodium hyaluronate has been touted to promote joint lubrication, increase endogenous production of hyaluronate, decrease prostaglandin production, scavenge free radicals, inhibit migration of inflammatory cells, decrease synovial membrane permeability, protect and promote healing of articular cartilage, and reduce joint stiffness and adhesion formation between tendon and tendon sheaths. The molecule lines the synovial membrane and acts like a sieve, excluding bacteria and inflammatory cells from reaching the synovial compartment by steric hindrance. The actions of exogenous and endogenous hyaluronan appear to be similar. At the present time, sodium hyaluronate is generally recommended for mild to moderate synovitis and capsulitis, rather than DJD. The drug appears to have a chondroprotective effect, but it is unclear whether this is a direct effect or as a result of its effect on the articular soft tissues. Sodium hyaluronate is administered intraarticularly or intravenously. Hyaluronate was used in experimental dogs at a dose of 7 mg per joint, intraarticularly, once weekly with success in slowing DJD.

REFERENCES

1. Beale BS. Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats. In: Mandelker L. Vet Clinics of North America. Saunders, Philadelphia; 2004:34:1: p 271-91.