SLOW-ACTING, DISEASE-MODIFYING OSTEOARTHRITIS AGENTS

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ORAL, DISEASE-MODIFYING OSTEOARTHRITIS AGENTS

A new concept in the management of veterinary osteoarthritis (OA) has emerged in the form of products that are administered orally. Unlike the parenterally administered products, which are at least partially purified and modified drugs, these oral products are considered to be nutritional supplements and do not require US Food and Drug Administration approval. The oral, disease-modifying OA agents are thought to have the same effects as parenteral disease-modifying drugs like polysulfated glycosaminoglycan (PSGAG; Adequan; Luitpold Pharmaceuticals, Shirley, NY); namely, a positive effect on cartilage matrix synthesis and hyaluronan (HA) synthesis by the synovial membrane and an inhibitory effect on catabolic enzymes in osteoarthritic joints. Oral, disease-modifying OA agents contain precursors for synthesis of hyaline cartilage matrix and are reported to provide these precursors in

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supraphysiologic quantities to diarthrodial joints. Their major advantage is ease of administration; however, controversy surrounds the efficacy of these agents, in part, over questions of bioavailability after oral administration. Studies investigating their efficacy for the treatment of OA in companion animals are not currently available.

**Composition**

The majority of nutritional supplements contain glucosamine and chondroitin sulfate (CS) in either purified, extracted, or complexed form. Two commonly used oral supplements are Glycoflex (Vetri-Science Laboratories, Essex Junction, VT) and Cosequin (Nutramax Laboratories, Baltimore, MD). Glycoflex is an extract from the *Perna canaliculus* mollusc exoskeleton which is reported to contain glucosamine and CS. Cosequin contains purified glucosamine, CS, and manganese ascorbate. Glucosamine is an ubiquitous amino monosaccharide (molecular wt, 179) used in the synthesis of disaccharide units of glycosaminoglycans. Glycosaminoglycans form the side chains of the core proteins of aggrecan (the large, aggregating proteoglycan) and biglycan, decorin, and fibromodulin (the small, nonaggregating proteoglycans) of articular cartilage. Glycosaminoglycans also form the repeating disaccharide units of HA. Tissues containing hyaline cartilage or mollusc exoskeletons are frequently used as a source of glucosamine. Glucosamine-based complexes include glucosamine sulfate, glucosamine hydroiodide, and glucosamine hydrochloride, each having similar bioavailability and efficacy.

CSs are glycosaminoglycans composed of alternating sequences of sulfated residues of uronic (β, D-glucuronic) acid and α, D-N-acetylgalactosamine linked by glycosidic β (1,3) bonds. The 4- and 6-sulfated forms with a heterogeneous molecular weight of about 10 kd are components of hyaline cartilage. Bovine trachea and nasal septum and shark skeletons are sources of CS for use in nutraceutical supplements. Manganese is a trace element and a cofactor in the biosynthesis of glycosaminoglycans. Ascorbate is a reducing agent for prolyl hydroxylase and lysyl hydroxylase, which catalyze the formation of hydroxyproline and hydroxylysine residues, respectively, in collagen. These residues are important in fibril formation and cross-linking in articular cartilage and the joint capsule, tendons, ligaments, and bone. Dogs produce their own ascorbate in the liver.

**Pharmacokinetics**

The bioavailability of orally administered amino sugars and glycosaminoglycans has hinged on the ability of glucosamine and CS polymers to traverse the gastrointestinal-blood barrier intact or as active subunits. Glucosamine is soluble in water and has a pK₆ of 6.91 at 37°C. Pharmacokinetic studies on glucosamine in man and the dog using ¹⁴C-
glucosamine have indicated that 54% of glucosamine is nonionized in the small intestine (assuming an intestinal pH of 6.8), yet most of the glucosamine is ionized in the acidic environment of the stomach. This creates a favorable condition for absorption from the small intestine but not from the stomach. Based upon fecal excretion, 87% of an orally administered dose of radiolabeled glucosamine was absorbed.

Oral absorption of CS has been reported in the rat, dog, and human, based on significant increases in serum levels of CS and 35S-labeled CS after oral administration of 35S-labeled CS. High molecular weight CS was detected in the blood, suggesting that some CS is absorbed intact. It is possible that absorption of 35S-labeled CS may occur separately from absorption of CS, because 35S-labeled CS can exchange with nonradioactive sulfate groups. Nevertheless, when both radiolabel and high molecular weight molecules elute together from a sizing column, there is reasonable evidence that the absorption has occurred with some of the molecules intact. Other evidence supporting absorption of intact CS is found when tritiated CS is administered to dogs. Tritium is less likely to exchange with hydrogen than 35S-labeled CS is with nonradioactive sulfate groups. When tritiated CS was administered orally to dogs, 70% of the radioactivity was absorbed, based upon fecal excretion tests.

**Mechanism of Action**

The proposed mechanism of action for oral supplements revolves partly around the disparity between cartilage synthesis and breakdown in OA. It is hypothesized that in OA, the demand for hyaline cartilage precursors, or "building blocks," is greater than the bodies' endogenous synthetic capability. This results in a diminished capacity for repair. Therefore, by providing these building blocks exogenously, the rate-limiting step of cartilage synthesis would be bypassed, allowing the body to counteract the degradative processes more efficiently and to reestablish cartilage homeostasis. The authors are unaware of data that corroborate the idea that chondrocytes in OA cartilage are nutritionally deprived, however.

Oral supplements may inhibit cartilage degradation in OA. In addition to its use in the synthesis of HA and glycosaminoglycans, orally administered glucosamine has been shown to stimulate glycosaminoglycan, proteoglycan, and collagen synthesis by chondrocytes and fibroblasts through an undefined mechanism. Glucosamine may have cyclooxygenase-independent, anti-inflammatory properties and may scavenge oxygen-derived free radicals and stimulate HA synthesis. Similarly, CSs have been shown to inhibit experimental histamine-induced inflammation, and cartilage degradative enzymes and to stimulate glycosaminoglycan and collagen synthesis.
Evidence for Efficacy

Although there are numerous anecdotal reports claiming improvement in mobility and pain reduction in dogs receiving oral, disease-modifying OA agents, there is no scientific evidence that these products are disease modifying in the OA companion animal. One study has demonstrated increased serum glycosaminoglycans, increased biosynthetic activity of chondrocytes, and decreased proteolytic degradation of cartilage explants in vitro using the serum of dogs given Cosequin for 1 month. A prospective study using Cosequin in the treatment of OA in horses showed statistically significant improvement in lameness in horses receiving the compound, as assessed by lameness score, flexion test, and stride length. Most of the evidence of efficacy used by manufacturers to support sales of their products comes from human clinical trials in Europe and South America. One study of 1208 patients reported a “good” therapeutic efficacy in 59% of patients and a “sufficient” response in another 36%. Two other studies showed a favorable response in comparison to ibuprofen, and another demonstrated histologic reversal of cartilage degradation after glucosamine administration.

Safety

A recent study assessing normal dogs given Cosequin over a 30-day period showed statistically significant but clinically irrelevant changes in hematologic and hemostatic effects, most notably in platelet function tests. Human patients receiving glucosamine or CS showed a high degree of tolerance, with a “full tolerance” rate of 86% of human patients receiving oral glucosamine. In this study, 2.5% of 1208 patients were considered to be “intolerant,” with gastrointestinal complaints (that is, diarrhea) being the most common cause of product discontinuation. In dogs and mice, no adverse effects were noted, even with chronic (>1 year) oral administration. No median lethal dose for CS could be established in mice, even when given saturated solutions of CS, and no adverse effects were observed in dogs given 500 mg of CS orally for 1 year. Oral, disease-modifying agents appear to be safe, but long-term veterinary studies are warranted.

Summary

Orally administered, disease-modifying agents are safe, cross the gastrointestinal tract, and their components may modify the painful clinical signs of human and animal OA. Currently, only anecdotal reports are available relating to the clinical use of these agents in the treatment of small animal OA. Although these testimonials are encouraging and the products are extensively used, scientific evaluation of
their efficacy in vivo will be difficult but necessary to substantiate their efficacy.

HA

Although there is clinical research regarding the use of HA in equine OA, there is little information regarding its use in the companion animal. Literature on the use of HA in the dog arises from its use in experimental animal models of OA rather than clinical trials. For a complete veterinary review, the reader is referred to Howard and McIlwraith.

Components

HA, which is also known as hyaluronic acid and sodium hyaluronate, is a linear polydisaccharide. It is a polyanionic, nonsulfated glycosaminoglycan consisting of repeating disaccharide units of D-glucuronic acid and N-acetylglucosamine linked by (1,3) glycosidic bonds. These units are then linked by (1,4) glycosidic bonds to form long, unbranched chains consisting of between 10,000 and 20,000 disaccharide units. At physiologic pH, it is properly named hyaluronate, as it is then anionic and associated with monovalent cations. When the cation of the polysaccharide is undetermined, the compound can be referred to as HA.

The average molecular weight of synovial fluid HA is estimated to be between 2 and $6 \times 10^6$ d in humans and animals. HA is a major component of synovial fluid and interacts with aggrecan monomers through a noncovalent association stabilized by link protein to produce the large, aggregating proteoglycans in articular cartilage. Due to its presence in synovial fluid, cartilage, umbilical cord, and vitreous humor, it is readily available for extraction and purification for commercial use.

Pharmacokinetics

Although most formulations of HA are labeled for intra-articular use only, some products are available for intravenous use. The plasma half-life of HA in a rabbit model following intravenous injection is between 2.5 and 4.5 minutes, with both the liver and articular tissues capable of HA degradation. The half-life of exogenous HA administered intra-articularly into a normal equine joint is estimated at 96 hours, with similar results found in normal rabbit joints. Pharmacokinetics for either intra-articular or intravenous use in the dog are not readily available.
Mechanism of Action

The mechanism of action through which exogenous HA exerts its influence on the OA joint is speculative. One proposed mechanism is an effect mediated through increased viscosity of the synovial fluid, also known as viscosupplementation. It has been demonstrated that OA joints have decreased viscosity of synovial fluid. This decrease initiates or propagates a chain of events leading to or exacerbating degenerative changes, so that re-establishing normal viscosity may be beneficial in and of itself.6, 68, 70 HA is a viscoelastic polymer with pseudoplastic properties conferring upon synovial fluid its thixotropic nature. At low shear, synovial fluid is highly viscous and relatively inelastic, but at high shear, the solution is elastic with low viscosity due to the presence of HA.43 Other theories on the mechanism of action of HA include an anti-inflammatory property mediated through stearic exclusion of inflammatory cells and reactive agents due to the concentration of HA, scavenging of oxygen-derived free radicals,77 and direct chemotactic inhibition of lymphocytes, macrophages, and polymorphonuclear cells and their enzymes.7, 82, 79, 92 High molecular weight HA stimulates HA synthesis by fibroblasts and synovial lining cells.79

Evidence of Efficacy

Reports of clinical efficacy arise in the human and equine literature, where intra-articular administration of HA is commonplace. These studies report decreased pain scores, improved joint mobility, and improved performance.79 The reported effects of intra-articular HA in sheep included improved gait, as measured by force plate. Interestingly, these studies also revealed increased cartilage catabolism, as measured by gross, histologic, and biochemical markers.33, 34 Conversely, two canine studies using the Pond-Nuki model of stifle OA showed statistically significant, positive effects in morphologic, morphometric, and biochemical parameters in dogs receiving intra-articular HA.1, 80 On atrophied canine articular cartilage, HA showed a "chondrostabilizing" effect hypothesized to act through down-regulation of tumor necrosis factor-α.24 Although there is significant controversy over the superiority of high versus low molecular weight HA, recent evidence supports a pharmacologic rather than physical effect, whereby both forms of the product are beneficial.6

Safety

Intra-articular administration of HA in humans met with a high degree of tolerance and a low incidence of adverse effects.79 No significant differences in hematologic parameters were noted in one human study, and most adverse effects are local in nature and attributed
to the administration technique instead of the product, but protein contamination cannot be excluded.

Summary

Based on information derived from use in other species and limited reports of use in the dog, intra-articular administration of HA is a potential form of therapy for canine OA. There is no information available regarding safety or efficacy of intravenous HA use in the dog.

PSGAG

PSGAG (Adequan, Luitpold Pharmaceuticals, Shirley, NY) has been available in Europe (Arteparon, Luitpold-Werk, Munich, Germany) since the mid 1960s. The reader is referred to recent reviews on PSGAG and to a complete listing of references. 19, 96, 98, 104

Components

PSGAG is a mixture of highly sulfated glycosaminoglycans composed mostly of CS and is extracted from bovine trachea and lungs. It has a size distribution of 2 to 16 kd and a relative mass of 6 to 7 kd. 19 There are an average of 3.25 sulfate groups per repeating disaccharide unit of CS. PSGAG binds to connective tissue, presumably because of the high negative charge of its sulfate groups. It is licensed for intra-articular (250 mg/mL) and for intramuscular (500 mg/mL) use in horses and is pending licensing for use in dogs in the United States. It is licensed for use in dogs in Canada.

Pharmacokinetics

Biochemical and autoradiographic evidence has shown incorporation of PSGAG into articular cartilage and meniscus following injection of PSGAG into joints. 46, 68 Tritiated PSGAG reached a concentration of 1.45 μg/kg in human articular cartilage and meniscus, roughly three times the concentration in serum after intramuscular injection. This concentration of PSGAG in cartilage should be high enough to inhibit proteinase activity. Binding of tritiated PSGAG to proteoglycans, collagen, and noncollagenous proteins was demonstrated in extracts of tissues from rabbits injected with PSGAG. 4 Following a single intramuscular injection of tritiated PSGAG into horses with osteochondral defects in the radial carpal bone, the radiolabel was detected in serum, synovial fluid, and articular cartilage.
Mechanism of Action

Anabolic effects of PSGAG have been demonstrated on articular cartilage explants and isolated chondrocytes and synovial fibroblasts, but results have been inconsistent (see Burkhardt and Ghosh for review and references). PSGAG stimulated dose-dependent incorporation of \(^{35}\)S]methionine into protein by isolated canine chondrocytes, whereas it did not affect incorporation of \(^{3}H\)thymidine into DNA. This suggests that PSGAG stimulates synthesis by existing chondrocytes and not by cell replication. Keratan sulfate (a marker of the chondrocyte phenotype) content was high in canine chondrocyte cultures treated with PSGAG, suggesting increased synthesis. Caron et al reported that PSGAG caused a reduction in proteoglycan synthesis by normal and OA equine cartilage explants. In contrast, Glade reported that PSGAG stimulated net collagen and glycosaminoglycan synthesis in normal and OA equine cartilage. An increase in the concentration of HA in synovial fluid has been reported as a result of treatment with PSGAG in humans, pigs, and horses.

PSGAG decreases cartilage catabolism. The activity of anaphylotoxins C3a and C5a (inflammatory mediators that are products of complement activation), reported to be present in OA joints, was inhibited markedly in vitro by PSGAG. The action of enzymes released from polymorphonuclear leukocytes was inhibited by PSGAG in a dose-dependent manner. Destruction of proteoglycan and collagen in cartilage of OA joints can result from the direct action of neutral matrix metalloproteinases (for example, stromelysin and collagenase) or intracellular lysosomal enzymes. PSGAG ameliorated the degradative effects of these enzymes on articular cartilage in vitro. The negatively charged sulfate groups on PSGAG are thought to react with the positively charged amino acid residues on proteins, including the neutral metalloproteinases, thus inhibiting their activity.

In the Pond-Nuki model of canine OA, concentrations of active and latent collagenase in the cartilage of PSGAG-treated dogs were lower than those in control cartilage. Treatment with PSGAG was associated with decreased concentrations of active neutral metalloproteinases in cartilage in a partial medial meniscectomy model of OA in rabbits. PSGAG inhibited enzyme production by equine synovial lining cells.

Yovich et al and Trotter et al found no histochemical evidence that intra-articular PSGAG (250 mg once weekly for 5 weeks) influenced the reparative process in experimentally induced partial- or full-thickness articular cartilage defects in horses. When PSGAG was used immediately postoperatively, osteochondral repair tissue in pony carpal joints injected with PSGAG was more fibrous than hyaline, suggesting that immediate postoperative use of PSGAG may be contraindicated when osteochondral defects are present. In this study, there was no protective effect against development of mechanically-induced "kissing lesions."
Evidence of Efficacy

PSGAG had a disease-modifying effect on cartilage homeostasis in models of OA, based on decreased microscopic structural alteration, retention of proteoglycan in cartilage, and decreased proteinase activity when compared with activity in control joints. In equine joints injected with monoiodoacetate (a cytotoxic chemical), PSGAG had a disease-modifying effect on articular cartilage, as evaluated histologically, when administered intra-articularly (250 mg weekly for 5 injections) but not when given intramuscularly (500 mg twice weekly for 7 injections). Keratan sulfate concentration was significantly decreased in the synovial fluid from joints of unexercised ponies with osteochondral defects that were treated with intra-articular PSGAG, suggesting that PSGAG protected against loss of proteoglycan from the articular cartilage. PSGAG partly ameliorated carpal OA in pony joints with osteochondral defects.

When PSGAG (5 mg/kg twice weekly given intramuscularly) was given to very young dogs predisposed to hip dysplasia, the treated dogs had significantly better radiographic hip conformation than did untreated control dogs. On the basis of a total score for gross pathologic and cartilage biochemical measurements of OA, there was a disease-modifying effect of the drug in this study.

A multicenter, dose-response, clinical study in dogs with hip dysplasia and OA failed to show a significant beneficial effect of treatment with PSGAG. In horses, total protein concentration was lower and viscosity was higher in synovial fluid of horses with clinical evidence of joint disease that were treated with PSGAG. Intra-articular injection of PSGAG at doses of 250 mg and 500 mg weekly for 4 weeks attenuated the clinical signs of experimental inflammatory carpal arthritis in horses and improved the quality of the synovial fluid in horses with clinical joint disease.

Dosages

A variety of dosages have been used experimentally in in vivo models of canine OA. Based on the work of Lust et al in growing, hip dysplastic-predisposed dogs, the authors currently use PSGAG at a dose of 5 mg/kg administered intramuscularly twice weekly in dogs with OA. Near the end of this regimen, the authors introduce oral glycosaminoglycans in the form of Cosequin at the manufacturer’s recommended dosage. It should be remembered that Lust et al injected hip dysplasia-prone dogs from the age of 6 weeks to 8 months so that the drug was administered in the incipient stages of the development of OA; therefore, results in dogs with established OA may differ.

Safety

PSGAG has heparinoid activity and it increases the activated partial thromboplastin, prothrombin, activated clotting, and bleeding times
when administered to dogs, cats, and ponies. Administration of PSGAG to animals with a history of hypersensitivity, in shock, or with bleeding tendencies is contraindicated. Thrombocytopenia, sudden death, and minor side effects have been reported in human patients treated with PSGAG. Hamm et al reported that 1250 mg of PSGAG given intra-articularly to six horses once a week for 18 weeks did not cause adverse reactions. Adverse reactions in dogs treated chronically have not been reported.

Summary

Administration of PSGAG is a useful adjunctive treatment for OA in companion animals, but it is not a panacea. PSGAG is beneficial in the prevention and treatment of experimentally induced OA and in modifying progression of degenerative change in puppies predisposed to hip dysplasia. The literature indicates that the earlier the drug is administered the more likely it will decrease synovitis and protect against cartilage degradation in OA.

PENTOSAN POLYSULFATE

Pentosan polysulfate (PPS) is another disease-modifying, anti-OA drug that can be given by injection or orally. Unlike PSGAG, HA, and Cosequin, PPS is not derived from animal sources. Because PPS is not readily available or approved for use in dogs in the United States, the authors provide only a brief summary of its effects on the OA process. In Australia, PPS is marketed as Cartrophen Vet (Biopharm, Pty, Sydney, Australia). The reader is referred to the review on PPS by Little and Ghosh for a detailed analysis of the effects of PPS.

Components

The backbone of PPS is isolated from beechwood hemicellulose and consists of repeating units of xylanopyranoses that are sulfated synthetically. It has an average molecular weight of 5700 d.

Pharmacokinetics

Most of the effects of PPS on articular cartilage and synovial joints that are attributed to PSGAG apply also to PPS. In its calcium derivative, 10% to 20% is absorbed following oral administration in the rat, making it attractive for clinical use in the dog and cat. It has been used extensively in Europe for thrombosis and hyperlipidemia in humans, but its application in the treatment of OA is recent. On the basis of its
antithrombotic and fibrinolytic effect, it may improve subchondral and synovial membrane blood flow in OA.  

**Mechanism of Action**

PPS modulates cytokine action and preserves proteoglycan content in animal models of OA, and increases the molecular weight of HA in synovial fluid from rheumatoid human joints. It cofractionates with high molecular weight extracts of articular cartilage and meniscus from rats following intra-articular injection, suggesting uptake by these tissues. PPS may bind to the cell membrane (possibly through interaction with cell surface glycoproteins like thrombospondin) and may be internalized by pinocytosis.

**Evidence for Efficacy and Safety**

In the Pond-Nuki model of OA in dogs, PPS administered at 2 mg/kg intramuscularly once weekly for 3 weeks resulted in significantly decreased articular cartilage damage, based on gross and histologic evaluation and maintenance of normal articular cartilage proteoglycan content. Two clinical trials of PPS in dogs have been reported. Read et al described 40 dogs with single or multiple joints affected with chronic OA that were treated with PPS subcutaneously for 4 weeks. Half of the joints were hips. Dogs receiving PPS had an overall favorable response to treatment, based on lameness, body condition, pain on joint manipulation, and willingness to exercise. The best response was observed at a dose of 3 mg/kg. Dogs with fragmented medial coronoid process or osteochondritis dissecans of the elbow were treated in a prospective, randomized study with either 3 mg/kg of PPS administered intramuscularly or by standard surgical intervention. Based on force plate evaluation, a more rapid return to function was observed in the PPS-treated group, and at 9 months, there was no difference between groups in the gait parameters measured. It remains unknown if the drug-treated group would remain the same clinically over a life span as the surgically treated group. Few complications of PPS use have been reported. It will increase clotting profile times, prolong the action of antithrombin III, and may cause thrombocytopenia, presumably through interaction with platelet receptors.

**Summary**

PPS has pleiotropic effects on joint tissues, ameliorates articular cartilage degeneration, and is therefore a potentially useful adjunct in the prevention and treatment of OA.
The tetracycline antibiotics are broad-spectrum bacteriostatic agents produced by various species of *Streptomyces* organisms. Included in this group are tetracycline, oxytetracycline, chlortetracycline, doxycycline, and minocycline. The tetracyclines have been used extensively in veterinary medicine for treatment of a wide variety of conditions caused by gram-positive and gram-negative bacteria, chlamydia, mycoplasma, rickettsia, spirochetes, and some protozoa (*Haemobartonella*). Tetracyclines are believed to have activity beyond their antimicrobial action, including the ability to decrease bone loss associated with periodontitis and potentially to provide a disease-modifying effect in both rheumatoid arthritis and osteoarthritis.

**Pharmacokinetics**

Doxycycline and minocycline are more lipid soluble than other tetracyclines, are absorbed well from the duodenum, and have good distribution to various body tissues. Over 95% of doxycycline is absorbed from the duodenum. The elimination half-life of orally administered doxycycline polyphosphate is approximately 12 hours. Unlike other oral tetracyclines, doxycycline is excreted into the feces in an inactive form by the small intestine. Due to its high degree of absorption and subsequent excretion in an inactive form, doxycycline has less adverse effect on intestinal bacteria than some of the other tetracyclines.

**Mechanism of Action**

It has become clear that the biochemical activity within the osteoarthritic joint is not limited to products of the arachidonic acid cascade. Degradative enzymes, primarily metalloproteinases, have an important role in cartilage matrix degradation. Products of cartilage degradation are thought to incite the synovial response associated with OA, and this, in turn, is associated with the inflammatory response due to the release of eicosanoids, cytokines, and other inflammatory mediators. Cytokines, including interleukin-1 and tumor necrosis factor-α, stimulate further release of metalloproteinases, thus perpetuating the cycle of degradation and inflammation. With possibly a few exceptions, nonsteroidal anti-inflammatory drugs do not affect metalloproteinase activity directly.

Matrix metalloproteinases are normally controlled by naturally occurring tissue inhibitors of metalloproteinase. In OA, an imbalance occurs between metalloproteinase activity and tissue inhibitor of metalloproteinase production, resulting in increased catabolism within the joint. It has been speculated that inhibition of metalloproteinase activity would
be beneficial for decreasing cartilage degradation during the course of OA. Tetracyclines, specifically doxycycline and minocycline, have been identified as having the ability to inhibit the activity of the metalloproteinases, collagenase, and gelatinase in vitro. The method by which the tetracyclines inhibit metalloproteinase activity is not certain, although there is evidence to suggest it occurs via chelation of the divalent cations necessary for metalloproteinase activity. Other possible mechanisms of action include inhibition of phospholipase A2, superoxide radical scavenging, interference with cytokine production, alteration of the immune response, and modulation of nitric oxide production.

Evidence of Efficacy and Safety

The prophylactic administration of approximately 1.75 mg/kg of doxycycline (twice a day orally for 8 weeks) to dogs undergoing cranial cruciate ligament transection resulted in decreased cartilage ulceration on the weight-bearing areas of the medial femoral condyle in treated dogs as compared with controls. Although doxycycline protected against cartilage ulceration, there was no difference in synovial thickening, ulceration of the medial trochlear ridge of the femur, or osteophyte production between treated and untreated dogs. The dogs tolerated treatment well with no vomiting or diarrhea noted. Collagenase and gelatinase activity in cartilage extracts from the treated dogs was significantly decreased compared with that of control dogs. There was little to no effect of doxycycline administration on proteoglycan synthesis in normal cartilage obtained from the same dogs. The same investigative group has reported a reduction in articular cartilage degeneration when doxycycline therapy was initiated 4 weeks after cruciate ligament transection, suggesting a therapeutic as well as prophylactic benefit to doxycycline administration. A radiographic study performed to evaluate progression of OA in dogs with naturally occurring OA secondary to cranial cruciate ligament rupture demonstrated no difference between treated and untreated dogs during a 52-week study.

Summary

There is evidence to suggest that tetracyclines have benefit beyond their antimicrobial activity. The ability to inhibit metalloproteinase activity may provide a disease-modifying effect in OA, and available data suggest that further investigation is warranted. Controlled, double-blind, prospective clinical studies have not been completed. The canine cruciate ligament transection model studies are frequently cited as the most convincing in vivo evidence of a benefit of oral tetracycline therapy for the treatment of OA. Until more evidence becomes available, the use
of tetracyclines as therapeutic agents for OA should be considered investigational.

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