Review of Physiology Modifiers: Hyaluronan, Polysulfated Glycosaminoglycan, and Tiludronate

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1. Introduction

Physiology modifiers, including hyaluronan, polysulfated glycosaminoglycan, and tiludronate, are meant to influence the cells within the musculoskeletal system. In this review, the general mechanisms of actions and indications are reviewed.

2. Hyaluronan

Hyaluronans have been used and studied in horses and humans since the 1970s. Most hyaluronan preparations are a 1% concentration with a molecular size of anywhere between 500,000 and 6,000,000 Daltons.1 Hyaluronan has been shown to interact with the CD44 receptor to modulate cell proliferation, migration, and gene expression. It has also been shown to decrease proinflammatory mediators and pain-producing neuropeptides that are common in the joint and lead to disease.2,3 In vitro, hyaluronan has shown a positive effect on chondrocyte morphology in articular cartilage explants,4 it stimulated proteoglycan synthesis in both chondrocyte and articular cartilage explant cultures,5 and it has also been shown to decrease prostaglandin E2 (PGE2) by synoviocytes in a lipopolysaccharide-stimulated model.6 Hyaluronan has also been shown to reduce shear strain after injury, probably leading to a decrease in post-injury trauma,7 and to have a positive effect when combined with corticosteroids such as with triamcinolone or methylprednisolone acetate.8,9 However, in vitro studies have shown mixed results in the face of corticosteroids, as one study showed little effect of hyaluronan on methylprednisolone acetate–induced articular cartilage matrix catabolism,10 and another showed that exogenous hyaluronan in combination with corticosteroids decreased the proteoglycan release typical of corticosteroid administration alone.11

There has also been some indication that molecular weight may have an influence on the efficacy of hyaluronan.2 One in vitro study showed that low-and medium-molecular-weight hyaluronan actually increased inflammation, whereas high-molecular-weight hyaluronan decreased inflammation. This was shown to occur via binding to the CD44 receptor and led to the conclusion that CD44 receptor may modulate inflammation via hyaluronan mass.12 Santangelo et al.13 showed that hyaluronan was protective of lipopolysaccharide-induced fibroblast changes in vitro and that high-molecular-weight hyaluronan had a greater effect than low-molecular-weight compounds. Although in vitro studies have shown an effect of molecular weight, variable effects

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in vivo studies have also been performed, evaluating the efficacy of exogenous hyaluronan on joints. Frisbie et al.\textsuperscript{18} showed that in an osteochondral fragment model, exogenously administered hyaluronan significantly reduced the histologic evidence of articular cartilage fibrillation, therefore imparting more of a protective effect on the articular cartilage than thought before. In addition, Gaustad et al.\textsuperscript{19} showed that hyaluronan decreased lameness at an effect greater than placebo administration. However, exogenously administered hyaluronan had no significant effects on an osteochondral defect model of the middle carpal joint compared with controls.\textsuperscript{20} Exogenous hyaluronan has also been shown to be beneficial when given systemically. Kawcak et al.\textsuperscript{21} showed that intravenous administration of hyaluronan resulted in decreased lameness in an osteochondral fragment model as well as reduced inflammatory signs within the synovial membrane and decreased synovial fluid total protein and PGE2 concentrations. Overall, the in vivo effect of exogenous hyaluronan has been good; however, in humans, the rate of local reaction after administration of intra-articular hyaluronan appears to be variable and at times fairly high (7\% to 53\%).\textsuperscript{22–26} There are no reports indicating the reaction rate of horses to exogenously administered hyaluronan; however, there has been a case report of severe reaction within 10 hours after injection of hyaluronan.\textsuperscript{27}

Exogenous hyaluronan has also been produced in an oral form. Although there is some concern about absorption and efficacy, Bergin et al.\textsuperscript{28} showed that in 24 yearlings with hock osteochondritis desicicans treated with 100 mg of oral hyaluronan per day for 30 days, effusion was significantly reduced compared with those that were not treated. Therefore, there is some indication that administration of oral hyaluronan can be efficacious. In a small clinical study, Carmona et al.\textsuperscript{29} showed a trend for exogenous oral hyaluronan to reduce effusion.

Overall, exogenous hyaluronan has been shown to be efficacious for use in treating horses with joint disease and appears useful for reducing articular cartilage fibrillation. However, large-scale clinical studies on the efficacy of hyaluronans for prevention of disease are lacking.

3. Polysulfated Glycosaminoglycans

PSGAGs have shown beneficial effects in vitro. Specifically, they have been shown to stimulate proteoglycan synthesis,\textsuperscript{30} increase collagen and glycosaminoglycan synthesis in vitro,\textsuperscript{31} and decrease PGE2 release in response to lipopolysaccharide in a synoviocyte model.\textsuperscript{32} However, the results have been variable in in vivo studies. PSGAG has been shown in vivo to have no significant effect compared with controls in an osteochondral defect model of the middle carpal joint.\textsuperscript{20} However, Frisbie et al.\textsuperscript{18} have shown that exogenously administered PSGAG decreased synovial effusion, subintimal fibrosis, and synovial membrane vascularity in an osteochondral fragment model. In addition, Gaustad et al.\textsuperscript{19} showed that PSGAG decreased lameness in comparison to placebo. However, Todhunter et al.\textsuperscript{32} showed that in an articular cartilage healing model, PSGAG administration decreased healing ability. Although in vivo effects appear to be variable, a survey of equine clinicians showed that PSGAGs are perceived to be moderately effective and even better than hyaluronan for subacute lesions.\textsuperscript{33} However, hyaluronan was perceived to be better than PSGAG in the acute stages of joint disease.\textsuperscript{33}

Overall, PSGAGs appear to be clinically beneficial for management of joint disease in horses, and recent evidence supports its use for reducing synovitis.

4. Tiludronate

Bisphosphonate compounds are meant to inhibit osteoclastic function and to have a mild anti-inflammatory effect. Tiludronate has been used in horses over the last 10 years. Although it was initially given at 0.1 mg/kg daily for 10 days, it has now been shown to be effective at a single 1.0 mg/kg dose. This is typically diluted in a 1-liter bag of saline given over 30 minutes. Most clinicians will premedicate with a dose of flunixin meglumine because in one early study, mild colic was seen in a low percentage of horses.\textsuperscript{34} An in vivo experimental study showed that in horses with osteopenia induced by lower-limb cast application, those horses treated with tiludronate had significant reduction in bone resorption, therefore leading to the conclusion that it had a protective effect on sparing bone density in this model.\textsuperscript{35} Otherwise, three clinical studies have led to the justification for the use of tiludronate in clinical situations. Deniox et al.\textsuperscript{36} showed that tiludronate administration improved lameness in horses with navicular disease, especially in those with an acute history of lameness development. In addition, Coudry et al.\textsuperscript{37} showed that administration of tiludronate in horses with osteoarticular lesions of the thoracolumbar vertebrae significantly improved dorsal flexibility in those horses that were treated. In addition, Gough et al.\textsuperscript{38} showed that administration of tiludronate in addition to a strict exercise regimen improved horses with clinical evidence of bone spavin.
Overall physiology modifiers appear to be clinically useful for joint disease. Although general application guidelines for these products can be taken from the literature, a personalized treatment program is usually used by different practitioners. Hyaluronans and PSGAGs are used both as preventative and for treatment of joint disease. Most practitioners probably use hyaluronans for synovitis and PSGAGs for more chronic conditions when articular cartilage damage is involved. However, when the literature is reviewed, they appear to have effects in both situations. Understanding of tiludronate use in the literature is reviewed, they appear to have effects in the treatment of hip osteoarthritis. Clin Rheumatol 2005; 24:244–250.

References and Footnotes


*aPSGAG: Adequan, Luitpold Pharmaceuticals, P.O. Box 9001, Shirley, NY 11967.*

*Tiludronate: Tildren, CEVA, 301 Route 17 North, Rutherford, NJ 07070.*