Practical chondroprotective drug use

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When confronted with a horse suffering from acute or chronic joint disease, your therapeutic goals should be aimed at both the soft tissue supportive structures and cartilage within the joint. The joint should not be thought of as simply articular cartilage, but rather as an organ consisting of cartilage, joint capsule, ligaments, synovial fluid and subchondral bone. Your therapeutic goals may be to decrease inflammation, alleviate pain or restore the articular environment to slow progression of disease. Your recommended therapy will likely include a combination of supportive care methods, as well as administration of pharmaceuticals and nutriceuticals.

Hyaluronan

Hyaluronan (HA) is present within articular cartilage where it is synthesised by chondrocytes and in synovial fluid where it is synthesised by type B synoviocytes. Hyaluronan can exist as hyaluronic acid, sodium hyaluronate or as hyaluronate depending on the environment in which it is found, and all terms are used interchangeably. It has been recognised for many years and in several species that in osteoarthritis (OA) the molecular weight and concentration of HA were diminished by one-half to one-third of their normal values, giving rise to the concept of visco-supplementation.

Hyaluronan imparts the viscoelastic nature to synovial fluid, which means it behaves as a viscous solution at low shear rates and is elastic in nature at high shear rates. In synovial fluid HA also lubricates the synovial membrane/cartilage interface (boundary lubrication) and physically excludes active inflammatory components and leukocytes from the joint cavity, a mechanism known as steric exclusion. Hyaluronan has additional direct anti-inflammatory effects and has been shown to decrease fibroblastic pannus formation in osteoarthritic joints.

The functional mechanisms of HA are directly dependent on the molecular weight and concentration of HA. This concept should be kept in mind when choosing from the assorted preparations of HA available for use. The molecular weight of equine synovial fluid HA has been reported to range between 2–3 million daltons, while the reported concentration of HA ranges between 0.33–1.5 mg/ml. For the available HA products, molecular weight and price are typically directly and positively correlated. Therefore, the high molecular weight preparations are recommended due to their increased efficacy and longer duration of action.

The various HA products have excellent safety profiles. Joint flares have been reported to occur in approximately 5% of injections. Joint flares can be difficult to distinguish from joint infection in the first 24 h and may require active treatment such as joint lavage, analgesics, NSAIDs and precautionary antibiotic administration. The clinical presentation of joint flares is typically milder than a joint infection with regard to joint swelling; lameness, synovial white blood cell count and joint flares are self-limiting. Joint flare also occurs subsequent to the administration of steroids.

The dosing routine for hyaluronan in horses has been arrived at based on clinical impressions, and there is wide variation in how horses respond clinically to HA administration. When administered for idiopathic synovitis, HA would typically be injected intra-articularly (i.a.) every 3–6 weeks for 3 injections. There is no rest period required after HA administration. It is common practice to administer corticosteroids with HA. Combinational therapy of HA/corticosteroid is recommended when treating synovitis that is minimally responsive to HA alone or when treating the coffin joint, which does not appear to respond clinically as well to HA therapy as other joints. The manufacturer recommended doses are based on use in a fetlock or carpus, so when using HA in a large joint such as a stifle, one should probably administer a double dose.

Polysulphated glycosaminoglycan

Polysulphated glycosaminoglycans (PSGAGs) are capable of stimulating chondrocyte metabolic activity while concurrently inhibiting the effects of many enzymes involved in cartilage breakdown. PSGAGs also stimulate HA synthesis by the synovial membrane, and have anti-inflammatory and analgesic properties. These beneficial effects on cartilage metabolism have been demonstrated in numerous species in both ex vivo and in vivo studies and in multiple types of naturally occurring and experimental joint diseases. Despite extensive research, the exact mechanisms of action of PSGAG remain unknown.

Originally, PSGAG was designed and evaluated for i.a. administration. When used i.a., PSGAG was administered at a dose of 250 mg weekly for a minimum of 3 weeks with good clinical results. However, it is well recognised that i.a. injection is potentiated by the administration of PSGAG. In order to circumvent potentially devastating iatrogenic i.a. infections, i.m. administration of PSGAG was evaluated. Following administration of 500 mg PSGAG i.m., therapeutic levels of PSGAG were found in multiple joints for up to 12 h. It is currently recommended that PSGAG be administered i.m. at 500 mg every 3–5 days for a minimum of 5 treatments. It is certainly safest to administer PSGAG i.m., however if one is going to administer PSGAG i.a., then an aminoglycoside (e.g. 250 mg amikacin) should be concurrently injected. While no studies have been performed to determine the effects of amikacin injection on PSGAG activity, there does not seem to be any decline in clinical responses.

Pentosan polysulphate

Pentosan polysulphate (PPS) was initially used in humans as an anticoagulant, then as an anti-inflammatory, and most recently...
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owners frequently report that their lame horse became sound and progression of articular cartilage erosion. In equine practice, horse tetracycline therapy include decreased joint pain and suppressed in humans. Clinical signs of improvement attributed to have long been advocated as treatments for rheumatoid and OA Tetracycline antimicrobials such as minocycline and doxycycline a veterinarian.

Nutriceuticals
There are numerous components recommended in the treatment of joint disease including: chondroitin, glucosamine, Perna mussel, ascorbic acid and omega-3 fatty acids. Few have been investigated in the laboratory and in thorough clinical trials. Because nutriceuticals are not drugs, they are not regulated by government agencies in most countries. When tested, the label claims and actual components of most joint supplements do not match. The equine formulation that has been most extensively studied is Cosequin (Nutramax). That is not to say that none of the other joint supplements work, but there is no way to determine if they will. One way to determine if a nutriceutical is efficacious is to suggest that a client start their animal on Cosequin to see the maximal effect that might be obtained. They can then change to a less expensive brand and use their judgement to see if it works as well. Cosequin does have 2 disadvantages: 1) it is expensive and 2) is only obtainable through a veterinarian.

Tetracycline family antimicrobials
Tetracycline antimicrobials such as minocycline and doxycycline have long been advocated as treatments for rheumatoid and OA in humans. Clinical signs of improvement attributed to tetracycline therapy include decreased joint pain and suppressed progression of articular cartilage erosion. In equine practice, horse owners frequently report that their lame horse became sound and ‘never went better’ when placed on doxycycline pending test results for Lyme Disease, despite the fact that the vast majority of those horses tested negative for Lyme Disease. The effectiveness of oral doxycycline and minocycline in the treatment of OA is due at least in part to the ability of tetracyclines to reduce matrix metalloproteinase (MMP) activity with joints through binding of the divalent cation zinc which is required to convert pro-MMP to active MMP.

In our laboratory, in vitro and in vivo studies were performed to assess the capacity for doxycycline and minocycline to alleviate cartilage degradation associated with treatment of catabolic mediators interleukin-1 (IL-1) and matrixmetalloproteinase-13 (MMP-13). Our studies indicate that both doxycycline and minocycline exert their primary effect on the synovium which in turn results in protection of the articular cartilage from the degradative effects both catabolic mediators IL-1 and MMP-13. Interestingly, our in vivo studies show that doxycycline accumulates in the synovial fluid to a greater extent than minocycline. Current studies are being performed to determine the minimal dosing regimen needed to achieve anti-inflammatory, but not antimicrobial levels in synovial fluid. The long-term effects of low-dose doxycycline on antimicrobial susceptibility and photosensitisation are unknown, but there are studies of people on long-term, sub-antimicrobial doses of doxycycline and minocycline with rare side effects reported. Tetracycline antibiotics are highly plasma protein bound and should not be administered in conjunction with other highly protein bound drugs such as phenylbutazone.

With any of the chondroprotection medications, it is important to assign a rehabilitation programme that includes corrective trimming/shoeing, a detailed exercise programme and weight loss if necessary in order to achieve maximal success.

Further reading