Proceedings of the 11th International Congress of the World Equine Veterinary Association

24 – 27 September 2009
Guarujá, SP, Brazil

Next Meeting:
Nov. 2 -6, 2011 - Hyderabad, India

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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, lubricate the joint, restore the articular environment to slow progression of disease, or (in rare cases) increase cartilage destruction to encourage ankylosis. Your recommended therapy will likely include a combination of supportive care methods, as well as administration of pharmaceuticals and nutriceuticals.

There are numerous supportive measures that are beneficial in the treatment of joint disease. These include a variety of leg wraps, cold hosing, hot packs, laser and magnetic therapy, acupuncture, and physical therapy. While all of these adjunctive therapies have their benefits, this lecture primarily focuses on the use of tetracyclines, stem cells, and platelet rich plasma (PRP) for osteoarthritis. Pharmaceuticals and more traditional joint medications will be covered by Dr. McIlwraith.

**Tetracyclines or chemically modified tetracyclines:**
Tetracycline antibiotics 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’s Disease, despite the fact that the vast majority of those horses tested negative for Lyme’s 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 activity with joints.

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). In the laboratory studies, cartilage was cultured with synovium to mimic the joint environment. 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 of 1/100 of the antimicrobial dose of doxycycline protects the synovium from both catabolic mediators IL-1, and MMP-13. The results suggest that minocycline is effective at lower concentrations than doxycycline. However, there are no studies in horses elucidating the pharmacokinetic parameters of minocycline, so extrapolation of our laboratory results to a clinically relevant antimicrobial dose cannot currently be made. Recent funding from the AQHA has been obtained to determine the pharmacokinetic of orally administered minocycline in horses and to determine the distribution to plasma, anterior chamber, CSF, and synovial fluid following dosing.

To determine how well orally administered doxycycline is distributed to synovial fluid, 5mg/kg doxycycline was administered PO BID (1/2 the recommended antimicrobial dose); blood and synovial fluid samples were obtained at several time points. By 1 hour after administration,
doxycycline was detectable in the synovial fluid. The concentration reached was well within the concentration required in the laboratory study to diminish the effects of IL-1 or MMP-13, but did not reach antimicrobial concentrations in either the synovial fluid or venous blood. Interestingly, doxycycline continued to concentrate in the synovial fluid unlike the typical distribution noted in plasma with a half-life of 12 hours. The long term effects of low-dose doxycycline on antimicrobial susceptibility and photosensitization 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.

Several companies are developing chemically modified tetracyclines (CMTs) for possible therapeutic applications. Chemical modification of tetracyclines (CMT) includes removal of dimethylamine, methyl, and/or hydroxyl side groups. These modifications do not diminish their MMP inhibitory properties but do eliminate all antimicrobial properties of tetracyclines. Potential advantages of using CMTs compared to tetracyclines include more specific determination of mechanism of action (selective MMP inactivation), abolished potential for development of antibiotic resistant bacterial strains, fewer treatment-associated side effects, and a longer half-life in serum than tetracyclines.

Present clinical recommendations:
The lowest possible dose of doxycycline for use in OA is not presently known. There are also many reports of the use of low-dose doxy for laminitis and caudal heel pain. Based on the in vivo data, our current clinical recommendations include:
Week 1: 5 mg/kg PO SID.
Week 2: 5 mg/kg PO every other day.
Week 3: 5 mg/kg PO every 3rd day.

As with any medication, it is important that everything else be held constant, exercise, turn out, riding time and intensity, etc. Many horses can seemingly be maintained on every 3rd day doxycycline, but if the clinical effect is lost, then we typically suggest that they start the course over, but abbreviate each time period to 3 days (i.e. 3 days of once daily, 3 days of every other day). It is worth stating again that tetracycline antibiotics are highly plasma protein bound and should not be administered in conjunction with other highly protein bound drugs such as phenylbutazone.

Stem Cells for treatment of Joint Pain:
There are anecdotal reports of the use of stem cells (mostly bone marrow derived MSCs, but some embryonic as well) for the treatment of joint pain. The thoughts behind stem cell therapy vary from the hope that stem cells will “home” or locate to damage cartilage areas, turn into chondrocytes and regenerate new matrix, or that stem cells will function in as disease modulating cells, perhaps through decreasing inflammation within an arthritic joint. It is too early to determine if either of these hypothesis are true and there are no animal studies that have been performed to support or refute the claims. The potential for stem cells to form calcified bodies within a joint is a safety issue that will need to be closely monitored and addressed prior to routine clinical application of stem cells for joint pain.
Platelet Rich Plasma for alleviation of Joint Pain:
Like stem cells, the use of platelet rich plasma (PRP) for treatment of joint pain or arthritis is quite new, but unlike stem cells, there is a rapidly growing body of literature to support its use. In animal models, PRP prevents progression of arthritis (Saito et al. Clin Exp Rheumatol 2009;27:201-207. In a retrospective cohort study in human beings with knee arthritis, PRP was significantly better than hyaluronic in reduction of pain and improvement of function (Sanchez et al. Clin Exp Rheumatol 2008;26:910-913). Although the molecular mechanisms behind the decreased pain and improved function are not well elucidated, one study suggests the PRP enhances the secretion of hyaluronan by synovial fibroblasts in arthritic patients. Zavadil also showed that application of PRP at the time of total shoulder arthroplasty significantly lowered post-operative pain scores and functional internal rotation index improvement factors (Savadil et al. J Extra Corpor Technol 2007; 39:177-182).

There are no clear guidelines for treatment protocols, but most studies use 3 injections at weekly intervals. The number of platelets or volume of injection is not well documented in most studies.

For the tetracyclines and the biologics PRP and stem cells, much more work is need to ensure safety, validate outcomes, and optimize treatment methods prior to routine clinical application.