Managing Joint Disease in the Racehorse in the Face of Stricter Drug Restrictions

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1. Introduction

Intra-articular use of corticosteroids has become a recent focus (or re-focus) of attention in the Thoroughbred racing industry. The clinical use and scientific basis of intra-articular corticosteroid administration including catastrophic injury, articular cartilage degradation, and the development of osteoarthritis (OA) as well as the timing of injection relative to racing have been reviewed.1 Most recently, there has been very specific examination by the Racing, Medication, and Testing Consortium (RMTC). At the time of that press release, the RMTC had approved (1) minimal withdrawal time recommendations for corticosteroids on the basis of both recently completed work funded in part by the RMTC and conducted at the University of Pennsylvania, University of California-Davis, Kenneth L. Maddy Laboratory, and HFL Laboratory-Kentucky and other corticosteroid research conducted both in the United States and abroad and (2) recommendations were developed during an RMTC-hosted Corticosteroid Experts Conference in Anaheim, California, on November 30, 2012. This meeting brought together qualified individuals with professional expertise in key areas with the goal of providing a comprehensive plan for regulating corticosteroid use in horse racing to protect equine health and welfare. Participants included analytical chemists, veterinary pharmacologists, veterinary surgeons, racing regulatory veterinarians, and practicing racetrack veterinarians. Among the recommendations was a prohibition on intra-articular use of corticosteroids within 7 days of a race, taking into consideration the concerns expressed by many participants about the proximity of intra-articular injections to race day. The experts also recommended a 72-hour withdrawal time for dexamethasone, a commonly used short-acting corticosteroid that can be administered intravenously, intramuscularly and orally. Other short-acting corticosteroids would have similar restrictions. It was also noted that the recommendations would fundamentally change the use of corticosteroids in veterinary practice in racing in the United States and therefore recommended a grace period to allow veterinarians time to adjust their veterinary practices and to allow trainers time to adjust their training practices to comply with the new regulations. Further details regarding these recommendations are discussed below (Table 1).

The purpose of this review is to offer possible modifications and alternatives with the intra-articular and systemic therapy for traumatic joint injury
and OA in the horse. Other countries have traveled down this pathway some time ago. More clear restrictions on the use of medication should be considered in the positive light that at the same time, there has been validation of non-corticosteroid treatments even in the acute stage of joint inflammation and newer biological therapies have emerged that have no side effects and offer positive advances.

2. Intra-Articular Corticosteroids: What Has Changed?
As discussed above, the RMTC issued a 7-day limitation for long-acting corticosteroids so that they would fall below their respective threshold levels regarding a series of experimental studies with intra-articular therapy.

After review of the data and addition of a tolerance interval for safety, the RMTC was able to calculate a recommended withdrawal time with the experimental dose of 100 mg of intra-articular methylprednisolone acetate (MPA) in one articular space, on the basis of a 95/95 tolerance interval, requiring approximately 16.6 days for the concentration of MPA in plasma or serum to fall below the 100 pg/mL threshold. This was rounded out to 21 days. In February 2012, Mid-Atlantic regulators, horsemen, and industry representatives met to discuss the implementation of numerous medication guidelines,

Table 1. Corticosteroid Threshold Chart

<table>
<thead>
<tr>
<th>Medication</th>
<th>Threshold</th>
<th>Minimum Withdrawal Time*</th>
<th>Route of Administration†</th>
<th>Experimental Administration Dosage‡</th>
<th>Withdrawal Time for 95/95 Tolerance Interval at Experimental Dose and Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>10 pg/mL of plasma or serum</td>
<td>7 Days</td>
<td>Intra-articular</td>
<td>Total of 9 mg of betamethasone (as a mixture of betamethasone sodium phosphate and betamethasone acetate) in one joint</td>
<td>7 Days</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>5 pg/mL of plasma or serum</td>
<td>3 Days</td>
<td>Intravenous, intramuscular, and oral</td>
<td>0.05 mg/kg of dexamethasone (as dexamethasone sodium phosphate)</td>
<td>3 Days</td>
</tr>
<tr>
<td>Isofluprodone</td>
<td>TBD</td>
<td>TBD</td>
<td>Intra-articular</td>
<td>20 mg total dose of isoflupredone (as isoflupredone acetate, Predef 2X) in one joint</td>
<td>Pending</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>100 pg/mL of plasma or serum</td>
<td>7 Days</td>
<td>Intra-articular</td>
<td>Total of 100 mg of methylprednisolone (as methylprednisolone acetate) in one joint§</td>
<td>21 Days</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>TBD</td>
<td>TBD</td>
<td>Intravenous and oral</td>
<td>Pending</td>
<td>7 Days</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>100 pg/mL of plasma or serum</td>
<td>7 days</td>
<td>Intra-articular</td>
<td>Total of 9 mg triamcinolone acetonide in one joint</td>
<td>7 Days</td>
</tr>
</tbody>
</table>

*The RMTC has recommended a 7-day regulatory withdrawal time for all intra-articular use of corticosteroids, recognizing that the clearance times for some will be longer than 7 days. Furthermore, this regulation is not in conflict with the withdrawal time for dexamethasone listed here; the use of dexamethasone intra-articularly is inappropriate because it would be considered off-label and a violation of the provisions of the Animal Medicinal Drug Use and Clarification Act (AMDUCA).
†Route of administration: Administration of these corticosteroids by other routes of administration may affect the length of time it takes before the medication is below the regulatory threshold (eg, betamethasone injected intramuscularly takes approximately 33 days for its plasma concentration to fall below the regulatory threshold). The withdrawal times for betamethasone, methylprednisolone, and triamcinolone acetonide apply to the intra-articular route of administration only and should not be interpreted as guidance for withdrawal of these substances after other routes of administration.
‡Administration dosage and related 95/95 withdrawal times: This is provided as guidance and does not constitute a guarantee. It does not account for repeat dosage, multiple articular site dosage, the effects of combining other medications with these corticosteroids, or different dosages from those listed here. A risk assessment must be done by the veterinarian and trainer to determine protocol that complies with the prohibition against administration of an intra-articular dose within 7 days of racing.
§Please note that for this dose of methylprednisolone acetate, a 21-day period from administration to racing is recommended to ensure that the medication is below the regulatory threshold. The minimum withdrawal time in this case anticipates the possibility of lower doses being used and assumes that these lower doses may decrease the length of time required for the concentration of the medication to fall below the regulatory threshold.
including the corticosteroid recommendations, on a regional uniformed basis. Numerous regulators and horsemen expressed concerns regarding the disparity between the 7-day ban on intra-articular use of MPA and the 21-day recommendation for the experimental dose to comply with the proposed regulatory threshold. There was a feeling from veterinarians as well that compliance with the recommendations would be difficult and could place horsemen and veterinarians attempting to comply with the recommendations in good faith in “harm’s way” and that the better approach may be to ban the drug and recommended use of alternative therapies. To continue the principal goal of the RMTC in having regulatory thresholds adopted and uniformity attained, a decision was made to remove methylprednisolone from the list of approved therapeutics.

3. Working Within the 7-Day Rule

As discussed in an earlier review, controlled studies have been performed in the horse to clarify therapeutic response as well as deleterious effects for betamethasone esters, MPA, and triamcinolone acetonide (TA). In a survey of AAEP members, a lower number of respondents were using MPA in high-motion joints (25.7%), with most (77.3%) opting for TA instead. A higher percentage (72.7%) were still using MPA in low-motion joints. In contrast to the published works documenting the negative effects of MPA, most respondents indicated that scientific papers and data determined their choice of corticosteroid use. The use of Depo-Medrol has decreased since demonstration of negative effects on the cartilage, but there is still considerable use. It is expected that the pragmatics of prolonged withdrawal time will further decrease the use of the drug. In addition to the options of betamethasone esters and TA as well as isoflupredone acetate, there are other medication options that are also presented below. A window into the future can easily be examined by looking at racetrack practitioners’ use in other countries. In the author’s native country of New Zealand, there is currently a 48-day withholding period for Depo-Medrol; personal communications indicate that there is no use of that drug in racehorses and that it is not missed. Racetrack practice has emerged with considerable TA use (withdrawal period is 4 to 5 days) and an increasing use of interleukin-1 receptor antagonist protein therapy in carpal, fetlock, and distal tarsal joints.

4. Hyaluronan

Combination therapy of corticosteroids and hyaluronan (HA) is quite common and can be defended scientifically. In an experimental study of equine osteoarthritis induced by osteochondral fragmentation in the middle carpal joint, eight horses received 20 mg of HA intra-articularly 14, 21, and 28 days after induction of OA. No adverse treatment-related events were detected. No changes in clinical signs were seen with HA compared with that in control horses, but, histologically at day 70, there was significantly less fibrillation with HA treatment compared with that in controls. The place for HA in combination therapy is therefore not as an acute anti-inflammatory but as a long-term disease-modifying osteoarthritis drug (DMOAD).

5. Polysulfated Glycosaminoglycan

Work examining the effect of intra-articular polysulfated glycosaminoglycan (PSGAG) suggests that this product has significant effects on acute synovitis and can be used in lieu of intra-articular corticosteroids. In a controlled study with the use of the equine osteochondral fragment–OA model, eight horses received PSGAG (250 mg) and amikacin sulfate (125 mg) intra-articularly at 14, 21, and 28 days after induction of OA, and eight control horses received 2 mL of saline (0.9% NaCl) solution and amikacin sulfate (125 mg) intra-articularly on study days 14, 21, and 28. The degree of synovial membrane vascularity and subintimal fibrosis was significantly reduced with PSGAG treatment, and there was a trend for reduced fibrillation at day 70. This indicated significant symptom-modifying OA effects as well as potential DMOAD effects. In other unpublished work, however, it was shown that the combination of triamcinolone acetonide and PSGAG was inferior to either triamcinolone acetonide alone or PSGAG alone and so current indications are that PSGAG, if used intra-articularly, should be used alone and not in combination with corticosteroids.

6. Extracorporeal Shock Wave Therapy

Evaluation of extracorporeal shock wave therapy (ESWT) in the osteochondral fragment model of OA also showed symptom-modifying effects in the carpal joint. Extracorporeal shock wave therapy has also been used to treat horses with OA. Horses were randomly allocated to receive local application of ESWT at days 14 and 28, a positive control therapy (intramuscular PSGAG), or sham ESWT (placebo). The degree of lameness in horses treated with ESWT improved significantly compared with the degree of lameness in placebo-treated or PSGAG-treated horses. No disease-modifying effects were evident in the results for synovial fluid, synovial membrane, or cartilage from the ESWT-treated or PSGAG-treated horses. There were no significant effects of ESWT on any bone variable, but serum osteocalcin concentration was significantly greater than in horses that received ESWT compared with placebo-treated control horses. The increase of serum biomarkers was indicative of bone remodeling, but there were no negative effects revealed. It could be concluded that ESWT is a viable non-pharmaceutical treatment for acute inflammation in equine joints.
7. Underwater Treadmilling
Aquatic therapy has become increasingly popular in its use for rehabilitation of equine musculoskeletal injuries. The mechanism of action of aquatic therapy and its potential use in the clinical management of equine OA has been recently reviewed. Recent human research has increased our understanding of neuromuscular responses to joint pain. Joint mechanoreceptors are characterized as sensory receptors within periarticular tissues that respond to changes in joint position and motion and are also important in regulating neuromuscular control associated with joint stability. Pain, inflammation, and joint effusion alter the normal sensory input from articular mechanoreceptors, which may cause motor neuron excitability and reduced muscle activation. Experimentally induced knee effusion produced significant quadriceps muscle inhibition. Joint instability alters the distribution of weight-bearing forces across articular surfaces and induces an increase in the recruitment of adjacent muscles to help aid in joint stability. The resulting functional imbalance and paired agonist-antagonist muscle groups contributed to increased joint instability and altered limb biomechanics, which leads to further progression of OA and chronic maladaptive compensatory mechanisms. There is an increasing perception among veterinarians that joint injuries may recur or be exacerbated as the result of muscle weakness, reduced joint range of motion, and poor proprioception, as exemplified by immobilization of the equine metacarpophalangeal joint. The entire musculoskeletal system must be rehabilitated to return the horse to optimal performance. Recently, the use of underwater treadmilling has been assessed in the equine OA model, and both decrease in osteoarthritis as well as improved proprioception were demonstrated. This is a clear demonstration that underwater treadmilling can be used as an adjunctive device for the treatment of traumatic joint inflammation, and there is no indication that it could not be used with a racehorse in full training.

8. Autologous Conditioned Serum (IRAP or IRAP II)
Autologous conditioned serum (ACS) was initially developed for the treatment of human OA as a product called Orthokine and was initially tested in horses in Europe and shown to be particularly beneficial in OA of the distal interphalangeal joint not responding to triamcinolone and HA. Orthokine was subsequently distributed in the United States as IRAP and in an experimental study was shown to provide benefit in osteochondral fragment–induced equine OA. Horses received 6 mL of ACS at 14, 21, 28, and 38 days after treatment (control horses received 6 mL of saline intra-articularly at the same time). Horses treated with ACS were observed to have significantly reduced lameness in the OA limbs even 5 weeks after the last treatment compared with placebo-treated horses. There was also a significant reduction in synovial membrane hyperplasia in treated compared with placebo OA joints at day 70 and a trend for improvement ($P < 0.10$) in cartilage gross score and cartilage histology noted in ACS-treated OA joints compared with placebo-treated OA joints. The hypothesis that the main effect of this new therapy was significant increases in interleukin (IL)-1 receptor antagonist protein (IL-1ra) was confirmed, with increases seen at days 35 and 71. A newer product, IRAP II, with a modified technique including a newly designed device with dual ports, has since been produced, and a comparative study was performed on the cytokine profiles of IRAP and IRAP II with the use of equine blood. Specifically, the level of IL-1ra in IRAP II was significantly increased compared with IRAP, and the ratio of IL-1ra to IL-1β also significantly increased in IRAP II compared with IRAP. On the other hand, there was a significantly increased level of tumor necrosis factor-α in IRAP compared with IRAP II but no significant difference in IL-1β levels. Production of insulin-like growth factor (IGF)-1 and transforming growth factor-β was both significantly increased over serum alone, and no significant difference between the two products was seen. On the basis of the extrapolation of doses used in this study, the recommendation for IRAP after arthroscopic surgery is 6 mL in knees, fetlocks, distal interphalangeal joints, and tendon sheaths but 10 to 12 mL in femoropatellar or femorotibial joints. Treatment in the latter joints would therefore require two preparations (two preparations of IRAP or IRAP II to give three injections at this dose rate).

The use of the IRAP products has considerably increased in racing jurisdictions outside the United States. They represent a specific biological therapy without negative side effects and have been well accepted by racing jurisdictions other than in Scandinavia, where there have been attempts to ban their use. There is no scientific validity to excluding such products from use in the competing athlete. In the 2009 joint therapy usage survey, sport horse practitioners were significantly more likely than racehorse or show horse veterinarians to use IRAP products ($P = 0.0035$ and $P = 0.04$, respectively), but this was in the United States. The author suggests that the use of IRAP in racehorses is used more often by racetrack practitioners outside of the United States.

9. Platelet-Rich Plasma
Platelet-rich plasma (PRP) has been advocated as a way to introduce increased concentrations of growth factors and other bioactive molecules to injured tissues in an attempt to optimize the local environment. There are various definitions of PRP, but the consensus now is that the product should have an increase in platelet content over the level in blood. The initial enthusiasm for PRP was based on growth factors within the α-granules including transform-
ing growth factor-β, platelet-derived growth factor-1, and IGF-2, fibroblast growth factor, epidermal growth factor, as well as endothelial growth factor. There are a number of other bioactive factors in PRP contained in dense granules of platelets, and there is an emerging paradigm that more than just platelets are playing a role in PRP.

The use of PRP to treat joint disease is currently increasing in the horse. Up until this time, the author has tended to recommend IRAP rather than PRP for treatment of joints. However, good clinical results with the use of PRP to treat OA in people have been reported, and recent in vitro work showed beneficial effects on cartilage metabolism.

More recently, a comparison between HA and PRP intra-articularly in the treatment of OA in the knee showed that local injection of a low-platelet-count PRP product had a significant effect shortly after the final infiltration and a continuously improved sustained effect up to 24 weeks Western Ontario and McMaster Universities Arthritis Index (WOMAC scores 65.1 and 36.5 in the HA and PRP groups, respectively, P < 0.001), in which the clinical outcomes were better as compared with HA-treated horses. Also in the HA group, the worst results were obtained for grade III gonarthrosis; whereas the clinical results obtained in the PRP group did not show a statistically significant difference with regard to the grade of gonarthrosis. The mean WOMAC scores for grade III gonarthrosis were 74.85 in the HA group and 41.20 in the PRP group (P < 0.001).

Along with this study, recent work has suggested that whereas higher numbers of platelets are seen in some PRP products, this brings higher white cell count levels and higher catabolic cytokine levels. In another study looking at the anabolic and catabolic activities of cartilage and meniscal explants in vitro and the effect of a single-spin PRP compared with a double-spin product, ADAMTS-4 gene expression was lowest for the single-spin PRP (ADAMTS-4 or aggregcanase 1 is considered a major factor in articular cartilage degradation). Also, radiolabel incorporation with 35-sulfate (an index of glycosaminoglycan synthesis) and 3H-proline incorporation (as an indication of collagen synthesis) were significantly enhanced with the single-spin system. Therefore, there is growing scientific support for the possible use of PRP after surgery, but we still need good clinical evidence in the horse.

At this stage, the use of PRP as a treatment for acute synovitis and capsulitis or early OA cannot be recommended.

10. Mesenchymal Stem Cells
The use of mesenchymal stem cells (MSCs) or mesenchymal stromal cells has become popular as an adjunctive therapy in equine orthopedics. Most work has concentrated on the multipotent cells present in adult bone marrow that can replicate an undifferentiated cell and have the potential to differentiate to lineages of mesenchymal tissue including bone, cartilage, muscle, ligament, tendon, adipose, and stroma. Multiple different pathways of multipotent MSCs and the proteins involved in their transcriptional control have been described in a review of MSC therapy in equine musculoskeletal disease. The clinical use of MSCs in horses, justification for their use, and issues surrounding their use have been reviewed. Early work with labeled MSCs has shown that they have an affinity for damaged joint tissue, and more recent work has confirmed their ability to localize and participate in the repair of damaged joint structures including cruciate ligaments, menisci, and cartilage lesions.

Most in vivo studies performed in animals other than horses are focused on meniscal repair. A particularly significant study involved direct intra-articular injection with beneficial effects to meniscus and secondary OA. This led to the initiation of a clinical study with intra-articular bone marrow–derived mesenchymal stem cells (BMSCs) plus HA therapy in clinical cases of femorotibial joint trauma. Meniscal injury (and other soft-tissue injury) with secondary OA is a common problem in our population of horses. It has also recently been demonstrated that experimental equine meniscal lacerations can be healed with equine BMSCs in fibrin glue and show increased vascularization, decreased thickness in repair, and increased total bonding. We also examined the use of BMSCs in the equine osteochondral fragment model. In a comparative study, it was shown that there was significant improvement in synovial fluid prostaglandin E (PGE2) levels with BMSC treatment and nominal improvement in symptom- and disease-modifying effects. On the other hand, there was an interesting negative response with adipose-derived stromal vascular fraction cells in that there was an increase in synovial fluid tumor necrosis factor-α levels and no significant change in PGE2 levels. The anti-inflammatory effect was another good example of trophic effects with MSCs. The term “trophic effects” applies to the observation that in addition to adult marrow–derived MSCs being capable of dividing and their progeny further differentiating into one of several mesenchymal phenotypes such as osteoblasts and chondrocytes, these MSCs also secrete a variety of cytokines and growth factors that have both paracrine and autocrine activities. These secreted bioactive factors suppress the local immune response, inhibit fibrosis (scar formation) and apoptosis, enhance angiogenesis, and stimulate mitosis and differentiation of tissue-intrinsic reparative or stem cells.

The trophic effects of BMSCs have been further demonstrated by a recent study in the horse in which an intra-articular injection of 20 million BMSCs in 20 mg of HA was compared with HA alone in the repair of full-thickness microfractured defects on the medial femoral condyle. There was enhancement of the firmness of the repair tissue at 6 and 12
months as well as a significant increase in aggrecan content in the repair tissue.

As a potential alternative for the use of acute traumatic synovitis and capsulitis, MSCs would not appear to be an option. There are good indications that MSCs have long-term effects for soft tissue inflammation within the joint as well as articular cartilage repair. The amount of DMOAD effects is less certain; their use is important in long-term regenerative therapies but not in the acute situation.

11. Systemic (Parenteral) Medications

Polysulfated Glycosaminoglycan

Polysulfated glycosaminoglycan administered intramuscularly is still very popular, but evidence is limited to anecdotal opinion. Intramuscular injections of 500 mg after surgery were commonly recommended by the author until a controlled study in experimentally induced equine OA showed no significant difference in the administration of intramuscular PSGAG (every 4 days for 28 days) as a positive control treatment in an evaluation of ESWT on experimentally induced osteoarthritis in the middle carpal joints of horses. Consequently, it is thought that the use of intramuscular PSGAG is very limited as a treatment. Any prophylactic value is still unproven.

Pentosan Polysulfate

Intramuscularly administered sodium pentosan polysulfate (NaPSS) has been commonly used outside the United States for the treatment of osteoarthritis as well as after surgery. Recently, NaPSS at a dose of 3 mg/kg intramuscularly at 15, 22, 29, and 36 days after induction of experimental carpal osteoarthritis caused a significant reduction in articular cartilage fibrillation and an increase in chondroitin sulfate 846 epitope (a synthetic biomarker) in the synovial fluid of both osteoarthritic and non-osteoarthritic joints. This indicated that NaPSS has some beneficial disease-modifying effects. The product is available in a 12-mL vial (which is the approximate dose for a 1000-lb horse), but caution must be exercised in the United States because the product is not licensed and is only available as an intra-articular lavage.

Intravenous HA

The use of intravenous HA (40 mg IV) after surgery is used by some clinicians, and there is scientific evidence that would support its use. With a study in the equine osteochondral fragment–OA model, three treatments of 40 mg were given intravenously 13, 20, and 27 days after osteochondral fragment creation. There was a significant decrease in lameness, synovial fluid protein and PGE2 levels, synovial membrane vascularity, and synovial membrane cellular infiltration at day 72 compared with the control group given 4 mL of saline intravenously at those same times.

Oral HA

A number of oral nutraceuticals are used after arthroscopic surgery. All these products are unlicensed, and, with the exception of oral HA, no scientific evidence has been produced to support their use. However, one oral HA product has been shown to benefit postoperative effusion after arthroscopic surgery for tarsocrural osteochondritis dissecans (OCD). Oral HA (100 mg) was given daily for 30 days after surgery in 24 yearlings (with 27 joints operated), and another 24 yearlings (30 joints operated) were treated with placebo daily for 30 days. An examiner blinded to the treatment groups scored the effusion at 30 days on a scale of 0 to 5. The mean 30-day effusion score in the treated group was 0.67 as compared with 2.05 in the placebo group ($P < 0.0001$).

References and Footnotes


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IN-DEPTH: RACING-RELATED LAMENESS


