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RMTC Position Statement on Corticosteroids

Introduction

Synthetic corticosteroids are important therapeutic drugs that are widely used in human and veterinary medicine for a number of indications including treatment of inflammation and pain associated with joint disease and arthritis. Corticosteroids were originally identified in the 1930s as the hormones produced by the adrenal gland that are necessary for the maintenance of metabolism, water balance, and electrolyte balance in mammals.[i] The anti-inflammatory properties of corticosteroids and their utility for the treatment of rheumatoid arthritis were discovered in the late 1940's. The 1950 Nobel Prize in Physiology or Medicine was awarded to researchers for the discovery of these hormones, their structure, and function.[ii]

Chemistry

Synthetic corticosteroids are structurally similar to hydrocortisone (cortisol) and cortisone that are produced primarily in the *zona fasciculata* and *reticularis* of the adrenal cortex of mammals. Hydrocortisone is released in response to stress and low concentrations of glucocorticoids in the blood. These substances possess increased glucocorticoid potency and efficacy and less mineralocorticoid activity compared to the endogenous hormones. Therefore, a smaller dose of synthetic corticosteroid needs to be administered and compared to administration of hydrocortisone or cortisone. Additionally, derivatives have been modified to produce long-acting formulations that enable less frequent dosing.

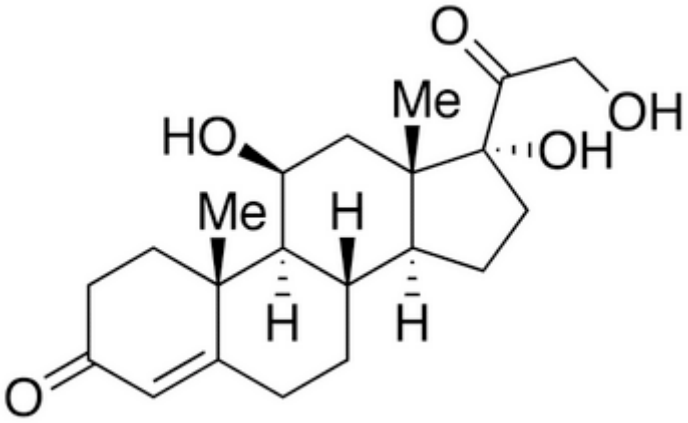

Figure 1. Chemical structure of hydrocortisone.

Corticosteroids with FDA-approved formulations available for intra-articular administration to the horse include methylprednisolone acetate, betamethasone acetate and phosphate, and triamcinolone acetonide.[iii] These products are administered as aqueous suspensions (methylprednisolone acetate and betamethasone acetate and phosphate) or solution (triamcinolone acetonide). Once solubilized in an aqueous environment, the ester must be hydrolyzed before the corticosteroid can cross the cell

membrane and bind to the appropriate receptors. Methylprednisolone is formulated as an acetate ester, which provides the longest duration of effect due to its poor solubility. Betamethasone is formulated as a mixture of the acetate ester and phosphate ester to produce immediate as well as long-lasting effects. Triamcinolone acetonide also provides long lasting effect. Of these, methylprednisolone acetate has been found to persist for the longest period of time in the equine joint. However the prolonged effects of corticosteroids are not all positive as they also have negative effects on the cartilage and bones of the joints that have to be weighed against the positive effects to make informed therapeutic decisions.

Pharmacokinetics

The elimination of synthetic corticosteroids following intra-articular administrations varies by steroid and can be vastly different from the rate of elimination following other administration routes.

Methylprednisolone Acetate

Research regarding the pharmacokinetics of methylprednisolone acetate was recently completed at the University of California – Davis. The research evaluated administration of methylprednisolone as its acetate ester in suspension into a single articular space at a total dose of 100 mg to a group of 16 exercised Thoroughbreds.[iv] Methylprednisolone reached maximum plasma concentration in an average of 0.273 days. Based upon this dosing regimen, plasma concentrations were below the limit of detection at 10 days in all horses with the average being 5.53 days and the range being 1.5-10 days. The limit of detection for methylprednisolone in plasma was 50 pg/mL. Urine concentrations resulting from dosing according to this protocol were measurable in some horses for more than 17 days.

In another study completed at The Ohio State University, researchers investigated the pharmacokinetics of a 100 mg or 200 mg dose of methylprednisolone as the acetate ester in suspension divided among several intra-articular spaces.[v] In this study, five exercised Thoroughbreds were administered a 100 mg intra-articular total dose then, after a washout period, were administered a 200 mg intra-articular dose. The 100 mg intra-articular dose was divided between the tarsometatarsal joint (60 mg) and the metatarsophanlangeal joint (40 mg). Based upon this dosing protocol, plasma concentrations were below 50 pg/mL at an average of 7 days. The higher dose of 200 mg was divided between the contralateral tarsometatarsal joint (80 mg), the contralateral metatarsophalangeal joint (60 mg), and one metacarpophalangeal joint (60 mg). The researchers found a statistically significant longer time between administration with the higher dose and the time that plasma concentrations were below 50 pg/mL. With a 200 mg total dose, the plasma concentrations were below 50 pg/mL at an average of 18 days.

Triamcinolone Acetonide

In a study published in 2013, researchers at the University of California – Davis reported on the pharmacokinetics of triamcinolone acetonide in 12 exercised Thoroughbred horses.[vi] In this study, researchers administered 9 mg of triamcinolone acetonide into the right antebrachiocarpal joint. Plasma concentrations after administration were below the limit of quantification (100 pg/mL of plasma) at 2.92 days in all horses studied and below the limit of detection (50 pg/mL of plasma) at 7 days in all horses.

In a 2011 study, researchers at the University of Pennsylvania investigated the pharmacokinetics of intra-articular injections of triamcinolone acetonide in 4 Thoroughbred horses.[vii] Each horse received

a 0.04 mg/kg (30 mg) intra-articular dose of triamcinolone acetonide in the left carpal joint. Plasma concentrations after administration were quantifiable in plasma for 102 hours post-administration.

Betamethasone

Intra-articular (fetlock) administration of 9 mg of a mixture of betamethasone sodium phosphate and betamethasone acetate to twenty Thoroughbred horses was investigated at the University of Florida and HFL Sport Sciences, Inc. in 2012. The study revealed that plasma concentrations of betamethasone peaked rapidly within 8 hours after administration due to the high aqueous solubility of the phosphate ester and that plasma concentrations remained detectable for ten days after administration. The method was characterized by a lower limit of quantification of 5 pg/mL and a limit of detection of 1 pg/mL. Plasma concentrations were less than the limit of quantification by five days after dose administration.

Pharmacodynamics

Corticosteroids are responsible for a variety of effects in the horse. Generally speaking, corticosteroids exert their effects by binding to receptors in the cytoplasm of cells that are present in many cell types throughout the body. The binding of a corticosteroid to a steroid receptor usually begins a sequence of events affecting gene transcription and the synthesis of proteins. Examples are:

- Potential alteration of the G protein-coupled receptors to interfere with intracellular signal transduction pathways
- Enhanced transcription in many genes, especially those involving suppression of inflammation.
- Inhibition of gene transcription – including those that encode pro-inflammatory substances.

The last two in this list are considered genomic effects. This type of corticosteroid effect usually occurs within hours to days after administration. The genomic effects outlast our ability to measure the synthetic corticosteroid in plasma, as evidenced by persistent suppression of the normal production of hydrocortisone following synthetic corticosteroid administration.[viii]

Therapeutic Use

Corticosteroids are used to reduce pain and swelling due to inflammation, and to alleviate allergic symptoms. They do so by suppressing the immune system. They do not, however, remove the underlying cause of inflammation if an anatomic initiator of inflammation is present; this is especially important in joints. Moreover, by removing the mediators of, and therefore the signs of, inflammation corticosteroids inhibit host defense and repair processes – thus interfering with the horse's natural identification of the need for healing if there is an anatomic reason for the joint inflammation, such as an injury to the bone or ligaments that must heal before normalcy can return. The corticosteroids can restore normal function to physiologic processes such as joint lubrication when disruptions of these normal self-defense mechanisms are initiated by trauma or overuse. They are also very effective at mitigating inflammation in cases of contact allergy such as contact dermatitis or lower airway disease; however they should not be used in lieu of removal of the primary cause.

Corticosteroids are often used in combination with other corticosteroids, hyaluronic acid, and other intra-articular treatments. The number of different protocols used by race track practitioners is extensive.

There is concern that repeated corticosteroid injections affect the articular surfaces of joints. In a 2010 paper, Dr. McIlwraith observed that intra-articular methylprednisolone acetate caused deleterious effects to articular surfaces.[ix]

Researchers at the University of Montreal investigated the effects of 3 injections of triamcinolone acetonide into a single radiocarpal joint in each of 10 horses. After measuring the various biomarkers of cartilage for 18 weeks, they observed significant differences in both treatment and control joints. Specifically, they found a significant increase in C1,2C (a marker for increased collagen cleavage); biomarkers CS846 and KS (biomarkers for aggrecan turnover); and CPII (a biomarker for type II collagen synthesis – which also demonstrated a significant difference in presence between treated and control joints). Based upon this, they concluded that administration of triamcinolone acetonide could cause increased collagen turnover in both treated and remote (*i.e.*, untreated) joints in the same horse.

In a 1994, researchers at Colorado State University created chip fractures of the distal radial carpal bones of twelve horses.[x] Six of those horses were subsequently treated with betamethasone acetate and sodium phosphate intra-articularly twice 21 days apart. While the difference between treated and untreated joints was not significant there was a trend toward increased pathologic changes in joints treated with betamethasone. Follow up studies have not been completed to determine whether that trend was an anomaly.

Finally, in Dr. McIlwraith's 2010 review of corticosteroids he observed that there may be some benefit to a period of rest occurring between intra-articular injections with any corticosteroid and racing.

AAEP Position on Use of Intra-Articular Corticosteroids in Performance Horses
The American Association of Equine Practitioners (AAEP) has adopted the following statement regarding the use of intra-articular medications in non-racing performance horses:

> *The AAEP recognizes that the judicious use of intra-articular medications with a valid veterinarian-patient relationship is appropriate treatment and can benefit a horse's health and well being. The AAEP defines this relationship to be a clinical or lameness examination with appropriate diagnostic tests prior to initiation of a therapeutic plan. Clinicians treating performance horses in the competitive environment are encouraged to develop treatment regimens, particularly with reference to the use of IA corticosteroids, which allow adequate evaluation of the horse's response to treatment prior to competition.*[xi]

RMTC Recommendations Regarding Use of Intra-Articular Corticosteroids
The RMTC invited a group of veterinarians and racing laboratory director with considerable expertise and experience in issues related to corticosteroids and horse racing in November 2012 to review the use of intra-articular corticosteroids in race horses. The goal of this meeting was to address concerns that had been raised by various groups regarding the potential overuse of corticosteroids in race horses. Paramount among the issues raised at this meeting was the need to curtail the practice of injecting one or more joints in a horse within a few days of racing. Accordingly, the group determined that it was desirable to set plasma or serum thresholds which would allow the practitioner to determine the horse's response to treatment prior to racing. The current ARCI Model Rule incorporates not only those thresholds but also a Restricted Administration Time (RAT). That RAT is based loosely upon the RMTC's recommended withdrawal guidelines.

The RMTC has recommended thresholds and withdrawal times for commonly used intra-articular corticosteroids that permit their use in accordance with the principles articulated by the AAEP in the above referenced position paper specifically with regard to the requirement to allow adequate evaluation of the horse's response to treatment prior to competition. Accordingly, the RMTC recommended a sufficient withdrawal period that the response to treatment could be evaluated before racing. This withdrawal period should be long enough that the systemic concentrations of the medication have dropped below the threshold and the amounts in the joint have declined enough that the horse will have time to again manifest signs of significant anatomic injury that might be dangerous during performance and that might be masked by the treatment. Seven days is a recommended safe withdrawal period with limited doses of intra-articular corticosteroids.

The necessary withdrawal period to stay under the plasma or serum threshold is lengthened with increased dosages and shortened with lower dosages. If the dosage used is higher (as with treatment of multiple joints) the withdrawal period must be lengthened to assure that threshold concentrations will not be violated. The recommended thresholds are based on scientific studies of the disposition of clinically used doses of the intra-articular corticosteroids that are commonly used to treat performance horses in the United States. The products, doses investigated, and their corresponding plasma or serum thresholds are as follows:

Product	Dose*	Threshold
Methylprednisolone acetate (*e.g.*, Depo-Medrol™)	**100 mg**	**100 pg of methylprednisolone per milliliter of serum or plasma**
Triamcinolone acetonide (*e.g.* Vetalog™)	**9 mg**	**100 pg of triamcinolone acetonide per milliliter of serum or plasma**
Betamethasone sodium phosphate and betamethasone acetate	**9 mg**	**10 pg of betamethasone per milliliter of serum or plasma**

*These are not clinical dosage recommendations; rather the dosages used represent those administered when making threshold recommendations

As noted in the specific sections regarding research on each of these intra-articular formulations above, the recommended withdrawal times generally exceed the time for the plasma or serum concentration in any horse to fall below the recommended threshold. Often the recommended withdrawal time exceeds the time to fall below the recommended threshold by several days. To determine RMTC withdrawal times, the European Milk withdrawal guidelines have been followed.

The purpose of using these guidelines is to provide a very conservative and safe threshold to trainers and veterinarians using approved therapeutic medications. This is a very robust statistical approach to determining withdrawal times and provides a wide margin of safety. The goal is to provide a safe withdrawal time to trainers and veterinarians which will provide a very small likelihood of a violation if dosing guidelines are followed and to assure that corticosteroid concentrations within joints have dropped below those that would mask anatomic injury that may be dangerous to the horse or rider/driver.

Genesis of the Issue

The use of corticosteroids in performance horses is, in some circumstances, dictated by trainers and based upon the entry of a horse in a race. This scenario emphasizes the masking of clinical signs

rather than the mitigation of disease. As such this process has the undesirable effect of increasing the danger of catastrophic injury to the horse and rider/driver if the treatment is too close to the performance event for the response to treatment and resolution of clinical signs to be evaluated. If the intra-articular concentrations remain so high that serious anatomic disruptions are masked, the probability of catastrophic injury greatly increases.

Representatives of the United States Trotting Association (USTA) and some other individuals recently raised the concern that use of the one-week RAT rather than threshold concentrations prevents therapeutic treatment of horses that race on a weekly basis – this includes some Thoroughbreds and Quarter Horses as well as most Standardbred horses. Representatives of the USTA requested that RMTC review the one-week RAT and related corticosteroid recommendations as they relate to the Standardbred business model of weekly races. The USTA has requested that the RMTC consider separate medication rules for Standardbred horses which allow them to be treated with corticosteroids within seven days of racing.

In response, the RMTC convened another meeting of experts with experience in treating and regulating the various breeds. The panel included practicing veterinarians in the Standardbred and Thoroughbred racing circuit; surgeons who treat a variety of racing breeds; and regulatory veterinarians with responsibility for regulating a variety of breeds in their jurisdictions. This white paper was produced by this second panel of experts to address the questions and concerns raised regarding corticosteroid use in the horse and the RMTC threshold recommendations.

Corticosteroid Concerns

Though needless degeneration of joints aided by injudicious use of corticosteroids is a long-term concern with the use of corticosteroids, it is the masking of the potential for catastrophic injury by the presence of pharmacologic concentrations of corticosteroids sufficient to hide early anatomic disruption that is of most concern. Use of corticosteroids close to time of the event in sufficient doses to hide these predisposing disruptions of bone and cartilage puts horses and people at increased risk of serious injury. It is this concern that drives the need to move treatment time and medication doses far enough away from the event to assure the horse is performing without joint concentrations of corticosteroids high enough to hide impending structural failure and its catastrophic consequences for the horses and people involved.

The threshold recommendations were chosen to assure this level of safety for the horse and rider/driver. Were this not a concern, the threshold concentrations could be more easily adjusted to accommodate different entry times and times between starts. But, concern for horses and people have dictated that the joint concentrations of the medication fall to those that give the horse the chance to show that there is more than just an inflammatory component to the injury in the evaluation of the response to treatment before performance recommended by the AAEP. This overriding concern, not laboratory limits of detection, was the basis for the selection of threshold concentrations recommended by the panel of veterinarians in 2012. This recommendation is based on current available science and needs to be assessed in light of practical application to the racing situation. This is the genesis for the concurrent recommendation of an implementation period for the new regulatory thresholds.

Summary of the Panel's Review of Key Discussion Points

1. **Are there physiologic differences between Standardbred and other breeds with regard to corticosteroids?**

The consensus of the group was that there are insufficient physiologic differences between Standardbred horses and other breeds to justify different regulations for use of the intra-articular corticosteroids based on breed. While these horses, because of their racing gait, tend to have fewer catastrophic musculoskeletal injuries than some other racing breeds, they nonetheless experience career -ending fractures and degenerative arthritis that, similar to other breeds, can be linked to excessive or injudicious corticosteroid use. The objective of the regulations is to protect the welfare of the horses and the integrity of the racing product. As such, the concerns extend beyond catastrophic injury and joint disease to the protection of the horse.

2. **Corticosteroids and Restricted Administration Times (RAT)**

The panel did recognize that RATs prohibit treatments with smaller doses of corticosteroids which would remain below the recommended thresholds but occur within 7 days of racing. This is not an issue that is unique to Standardbreds. Emphasis on thresholds rather than treatment times may be sufficient to allow a practitioner to observe a horse after treatment but prior to racing even without a bright line of a RAT. Practitioners must still allow several days between treatment and racing to avoid a high probability of a threshold violation. RATS that cannot be enforced by thresholds or other laboratory testing put trainers and veterinarians who attempt to abide by the medication rules at a competitive disadvantage and may put horses at risk. This conundrum warrants consideration in the final establishment of recommendations of thresholds or treatment times.

3. **Corticosteroids and Thresholds**

The RMTC has developed thresholds for regulating the intra-articular administration of the corticosteroids methylprednisolone acetate, betamethasone acetate and betamethasone sodium phosphate, and triamcinolone acetonide. Additionally, it is in the process of developing a threshold for regulating use of isoflupredone acetate. These thresholds have been reviewed by a variety of experts and were introduced to veterinarians at the AAEP Racing Committee meeting in December of 2012. At that meeting, several practitioners from Pennsylvania – including practicing Standardbred veterinarians - indicated that the thresholds were similar to those in effect in Pennsylvania and that they were using corticosteroids in accordance with the rules. Additionally, Minnesota has had similar thresholds for intra-articular corticosteroids in place since 2009 and the equine medical director has indicated compliance with their rules and a general ability to control excessive or injudicious use of corticosteroids.

4. **Implementation Period**

The RMTC Corticosteroid Experts previously recommended a corticosteroid rule implementation period during which trainers and veterinarians would be provided feedback regarding concentrations of corticosteroids in post-race samples before enforcement of corticosteroid thresholds would begin. The length of this implementation period may vary because different jurisdictions have different race meet schedules which may require a variety of time periods to implement the new thresholds. Ideally, the implementation period would be between three and six months in duration.

During this implementation period, trainers would not be assessed penalties for exceeding corticosteroid thresholds. Instead, both the veterinarian and trainer would be notified of the concentration(s) of corticosteroid(s) in each test sample in order to provide feedback to the veterinarian regarding which protocols comply with the regulations. This would allow veterinarians to adjust their practices and modify their protocols without risk of a positive finding, keeping in mind that the end goal is the safety of the horse and people.

Similar programs have been used in both Pennsylvania and Minnesota. In Pennsylvania, practitioners are have also been permitted to submit unofficial samples for specific corticosteroid testing after the rule went into effect for purposes of determining whether a protocol is acceptable. The results from these samples are reported directly to the submitting veterinarian. In Minnesota, practitioners were allowed to submit unofficial samples to the racing laboratory for analysis after corticosteroid administration. The practitioners were required to submit treatment records for the horse along with the sample. The laboratory would then screen the sample for the specific corticosteroid and inform the equine medical director for the commission and the veterinarian if the sample exceeded the threshold (concentrations were not provided). In 2013, after the practitioners adjusted their intra-articular corticosteroid treatment protocols, there were a total of 2 corticosteroid overages – one at the harness track and one at the Thoroughbred/Quarter Horse track. This was true despite the fact that many horses at both of these tracks compete every week.

California and Virginia have similar programs underway involving feedback to practitioners of results of tests performed on official samples. The equine medical directors are working with practicing veterinarians to evaluate withdrawal times for a variety of corticosteroid dosages and protocols for intra-articular injections completed as a part of routine practice.

Recommendations of the Panel

1. Corticosteroid thresholds should remain as recommended by the RMTC and enacted by the ARCI. This will protect horses, jockeys, and drivers by allowing veterinarians to evaluate the effects of treatment before racing.
2. RMTC should recommend that the ARCI remove the Restricted Administration Times from the regulations. The existing thresholds will prevent intra-articular administrations close to the race while allowing appropriate treatment with smaller doses of corticosteroids.
3. A commission-determined implementation period of approximately three to six months with feedback of laboratory results to practitioners is strongly recommended before any corticosteroid medication violations are prosecuted. This will allow veterinarians to adjust their protocols and adapt to changes in the regulations.
4. Continuing education should be provided to practitioners. Commissions are encouraged to direct practitioners to resources at the AAEP, RMTC, and the jurisdiction's Equine Medical Director.

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[i] Sneader, W., *Drug Discovery. A History*, John Wiley & Sons Ltd., West Sussex, England (2005).
[ii] Available online at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/.
[iii] Available online at: http://www.accessdata.fda.gov/scripts/animaldrugsatfda/.

[iv] Knych, H.K., *et al*, *Disposition of methylprednisolone acetate in plasma, urine, and synovial fluid following intra-articular administration to exercised thoroughbred horses*, J. vet Pharmacol. Therap. 2013 June 20. doi: 10.1111/jvp.12070 (2013) [Epub ahead of print].

[v] Menendez, M.I., *et al*, *Pharmacokinetics of methylprednisolone acetate after intra-articular administration and subsequent suppression of endogenous hydrocortisone secretion in exercising horses*, AJVR 73:1453-61 (2012).

[vi] Knych, H.K., *et al*, *Pharmacokinetics of triamcinolone acetonide following intramuscular and intra-articular administration to exercised Thoroughbred horses*, EVJ 2013 January 27, doi: 10.1111/evj.12059 [epub ahead of print].

[vii] Soma, L.R., *et al, Pharmacokinetics of intra-articular, intravenous, and intramuscular administration of triamcinolone acetonide and its effect on endogenous plasma hydrocortisone and cortisone concentrations in horses*, AJVR 72(9): 1234-42 (2011).

[viii] *Veterinary Pharmacology and Therapeutics, Ninth Edition*, p. 783.

[ix] McIlwraith, C.W., *The use of intra-articular corticosteroids in the horse: What is known on a scientific basis?* EVJ 42(6): 563-71 (2010).

[x] Foland, J.W., *et al*, *Effect of betamethasone and exercise on equine carpal joints with osteochondral fragments*, Vet Surg., 23:369-76 (1994).

[xi] American Association of Equine Practitioners, *Clinical guidelines for veterinarians treating the non-racing performance horse*, (2011).