Intra-articular corticosteroids are potent anti-inflammatory agents with prolonged effectiveness. Generalization about harmful effects of intra-articular corticosteroids is inappropriate, and research has defined differences in beneficial and deleterious effects. There is no evidence that intra-articular corticosteroids cause harm to subchondral bone or promote catastrophic injury. Sound evidence linking laminitis to corticosteroid injection of normal doses of corticosteroids is lacking. Author’s address: Gail Holmes Equine Orthopaedic Research Center, Colorado State University, 300 West Drake, Fort Collins, Colorado 80523; e-mail: wayne.mcilwraith@colostate.edu. © 2010 AAEP.

1. Introduction
The Thoroughbred horse-racing industry has come under renewed scrutiny in the last 2 yr in the United States because of horses suffering from catastrophic injury during high-profile events. Consequently, the public outcry from these events has led to Congressional oversight and investigation into the industry, which has led to significant scrutiny of medications that are used in the sport. Anabolic steroids have been banned in the last year and now, other medications are also being critically reviewed. Recently, intra-articular use of corticosteroids has recurred as a focus of attention. Proponents of intra-articular corticosteroid treatment argue that such therapy is needed to decrease inflammation and musculoskeletal pain, which is common in Thoroughbred racehorses, and more importantly, to avoid overloading of the other limbs, possibly leading to catastrophic injury. However, opponents of corticosteroid use feel that it is merely masking pain and results in joint deterioration. Much of this perception of harm is based on opinion and has been passed down through the literature.¹

The clinical use and scientific basis of intra-articular corticosteroid administration will be reviewed in this paper, including catastrophic injury, articular cartilage degradation, and development of osteoarthritis (OA) as well as the timing of injection relative to racing. This review was generated by a request by the American Association of Equine Practitioners Racing Committee and the Racing Medication and Testing Consortium (RMTC) to critically review the scientific data regarding intra-articular corticosteroids. A full manuscript is in press with Equine Veterinary Journal.²

2. Early History
The use of hydrocortisone in the treatment of a variety of musculoskeletal conditions in 94 horses and cattle was first reported in 1955.³ The author cited profound improvements in clinical signs in most cases but also cautioned that treated animals should be rested after injection to allow healing of affected tissues. This report was followed by a se-
eries of investigations by Van Pelt, Van Pelt and Riley, and Van Pelt et al.4–8 in the 1960s and early 1970s evaluating certain effects of various corticosteroid preparations in a wide variety of clinical conditions.4–8 A small number of clinical trials were also reported in the mid-1970s.9–13 Mostly favorable results were reported, but these studies were poorly controlled, and this compromised the interpretation of the results.

To the author’s knowledge, the first paper indicting corticosteroids as harmful in the horse was written by O’Connor in 1968.14 This was a review paper that addressed some important points but was based solely on human literature.14 The statement “an endless destructive cycle is set into motion which, if continued, will produce a steroid arthropathy which can render the horse useless” was referenced, and the reference was an abstract written by an anonymous author.15 In the chapter on steroid-induced, and the reference was an abstract written by an anonymous author which can render the horse useless” was referenced, and the reference was an abstract written by an anonymous author.

3. Early Evaluations of Direct Effects
A number of studies by Marcoux,17 Trotter et al.,18 Meagher,19 and Owen et al.20 were done to evaluate the effect of methylprednisolone acetate (MPA) injected into normal joints. These studies showed the deleterious effects of this corticosteroid.

4. More Recent Research on Beneficial and Deleterious Effects in Vivo and in Vitro
Controlled studies have been done in the horse in vivo to clarify therapeutic response as well as deleterious effects. Based on the author’s observation of an apparent lack of correlation between the prior use of betamethasone estersa and articular cartilage degradation during arthroscopic surgery for osteochondral chip removal in the early 1980s, experimental studies of the three most commonly used intra-articular corticosteroids, namely betamethasone esters, MPA, and triamcinolone acetonide (TA), were initiated using an osteochondral fragment model developed at Colorado State University (CSU).21–23 Examination of betamethasone esters showed that there were no deleterious side effects to the articular cartilage, and in addition, exercise did not have any harmful effects in the presence of corticosteroid administration. Subsequently, TA and MPA were evaluated in the CSU OA chip-fragment model. Examination of TA showed no deleterious effects and in fact, showed chondroprotective effects as well as therapeutic effectiveness, even when the corticosteroid was injected distant to the primary lesion in the opposite joint. In contrast with MPA, there was lowering of inflammation, but deleterious effects to the articular cartilage were present both with direct and remote injection. Protective effects of TA have also been shown in vitro.

There have been some opinions on low-dose administration alleviating the negative effects of MPA, but this has yet to be supported by scientific studies. It has also been shown in vitro that adjunctive use of hyaluronic (HA) with MPA does not mitigate the deleterious effects of MPA. However, the combination of TA and HA has been shown to be beneficial in humans, and such combination therapy is logical in the horse.

5. Laminitis—A Suggested Potential Complication of Intra-Articular Corticosteroid Use
Fear of laminitis has also caused less use of TA by some equine practitioners, despite scientific studies showing its effectiveness as well as its chondroprotective properties. There have been anecdotal associations made and maximum doses established based on an initial report of no cases of laminitis in 1,200 horses treated when a dose did not exceed 18 mg.25 A more recent publication provides the first follow-up study with data on the potential for TA to produce laminitis, and the conclusion was that there was no association between the occurrence of laminitis and the intra-articular use of TA.26 A relatively recent legal case in the United Kingdom where a horse developed laminitis after receiving 80 mg of TA in each tarsus and 20 mg of dexamethasone into its back27 led to the development of a review of the literature28 and a retrospective study of one clinician’s cases.29 The review of the literature revealed that substantial evidence linking laminitis to corticosteroid injection was lacking and that a large-scale multicenter trial was needed.28 In a third publication, the clinician reported that laminitis associated with intra-articular injection of corticosteroids had occurred in 3 of 2,000 (0.15%) cases. The majority of the time, TA was used in higher doses ranging from 20 to 45 mg.

6. Use of Corticosteroids in Low-Motion Versus High-Motion Joints
Another traditional concept has been that although it is better not to use MPA in high-motion joints, its use in low-motion joints (such as the distal tarsal joints) is appropriate. The implication has been made that we do not care about the state of the articular cartilage in these joints and that potentially promoting ankylosis is good. There is no evidence yet that we can promote ankylosis in this fashion, and the other side of this argument is that we should preserve articular cartilage whenever we can. A recent retrospective study of the effect of intra-articular treatment of OA in the distal tarsal joints with MPA or TA (with or without HA) led to a positive outcome in only 38% of horses.20 The entry requirement for the study was a 50% or better improvement after intra-articular analgesia. The authors recognized that because of diffuse analgesia, including the proximal suspensory area, some of the cases that did not respond may have had clinical problems other than OA of the distal tarsal joints.
Also, horses with OA of the distal intertarsal or tarsal metatarsal joint responded better than horses affected with disease in the proximal intertarsal joint. Horses treated one time with intra-articular MPA or TA either with or without HA improved after a median of 56 days ($p < 0.001$), and there was no significant difference between MPA and TA. These findings of observing clinical effectiveness at 56 days are supported by our studies with the CSU chip-fragment model, where effectiveness was still observed at day 70 when treatments with TA and MPA had been given at days 14 and 28.

7. The Association of Intra-Articular Corticosteroids and Catastrophic Injury

An interesting pathway of rationalization led to a concept that corticosteroids cause racetrack breakdown, more correctly considered as catastrophic injury.31 Although some histologic changes are seen in experimental research that are similar to early traumatic bone disease, these changes are very nonspecific and can hardly be extrapolated to the pathologic appearance of clinical traumatic lesions in the equine athlete. This argument is not to diminish the importance of catastrophic injury. It is a serious problem, and all possible pathogenetic pathways must be investigated. However, a role for osteochondrosis or corticosteroids in the pathogenesis of catastrophic injury has never been proven. Work by Kawcak et al.32 and Murray et al.33 refutes any harmful effects of TA or MPA on subchondral bone. It is now well-recognized that micro-damage in the subchondral bone occurs early in the exercising athlete, and this micro-damage can lead to pathologic fractures.34,35

8. Pharmacokinetics of Corticosteroids and Duration of Pharmacologic Effects

The anti-inflammatory actions of the glucocorticoids are mediated through cytoplasmic receptors.36 This, in turn, leads to gene-regulation changes and consequent changes in protein expression through signaling pathways. Equine veterinarians use corticosteroids for their anti-inflammatory effects, but this does not mean they are anabolic, as has been suggested by one author.37 That author’s contention was generated by extrapolation from the results of treating children during their growth period to adult horses; however, increased synthesis of critical components of the articular cartilage has been shown in association with TA and betamethasone injections.21,22

There are a number of pharmacokinetic studies being done with corticosteroids, but it is difficult, perhaps impossible, to directly transpose pharmacokinetic data into biological potency or activity. The latter depends on total dose administered, duration of action, duration of treatment, rate of conversion to biologically active metabolites, the crystal size of the suspension, and other difficult to define variables.38–40

9. Clinical Effectiveness (Pharmacodynamics) Relative to Pharmacologic Presence (Pharmacokinetics) and Potential to Quantitate this Activity

Results of in vivo studies have led to in vitro studies of the effects of corticosteroids on articular cartilage to identify specific cellular events. Measuring gene expression using pharmacogenomic methods, however, provides the potential of more global assessment of all pharmacodynamic responses after intra-articular corticosteroid injection. An example of this technique has been published using MPA administration in rats.41,42 In this study, MPA was administered using two routes, and the effect on mRNA gene expression from muscle cells was monitored over time using microarray technology. This work showed the ability of measuring gene expression (increased or decreased) as a pharmacodynamic (pharmacogenomic) method. As expected, a host of genes was differentially expressed, both increased and decreased as a consequence to corticosteroid administration. Also, differential gene expression occurred even after the pharmacokinetic effects were gone. This may explain why exogenous corticosteroids have both acute and chronic effects. It is proposed that using such methods in the horse would be a novel means of objectively evaluating pharmacodynamic effects relative to pharmacokinetics after intra-articular injection of corticosteroids in the horse. This would allow for the development of methods to not only better identify the significance of serum corticosteroid concentrations during routine drug testing but also help identify those cases that may be most responsive to treatment and most susceptible to laminitis; this may possibly lead to the development of drugs that may more specifically target the joint injury and disease.

10. Summary

1. Intra-articular corticosteroids are potent anti-inflammatory agents. Generalization about harmful effects of intra-articular corticosteroids is inappropriate, and research has defined beneficial and deleterious effects with different products. Betamethasone esters have no deleterious side effects and TA is, in fact, chondroprotective and can promote cartilage health, whereas MPA has been consistently shown to have deleterious effects.

2. Intra-articular corticosteroids have prolonged effectiveness in controlled studies in the carpal chip-fragment model documenting persistent clinical effects at 70 days after intra-articular therapy at 14 and 28 days.

3. Prolonged effectiveness of intra-articular corticosteroid administration is hypothesized to be because of the interaction with cytoplasmic receptors and the initiation of up-regulation of prolonged effects.
4. There is some evidence that a period of rest facilitates improved absorption of intra-articular corticosteroids and therapeutic efficacy, but exercise per se does not promote negative effects.
5. There is no evidence that intra-articular corticosteroids either cause harm to subchondral bone or promote catastrophic injury.
6. Substantial evidence linking laminitis to corticosteroid injection is lacking, and current clinical evidence argues against generalizations of potential risk.
7. There is no current evidence that combination therapy with HA can mitigate the negative effects associated with MPA, but recent work shows that HA does have chondroprotective effects. Long-term and combination therapy with TA or betamethasone esters is appropriate.

References and Footnotes


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*Depo-Medrol, Pharmacia and Upjohn Co., Kalamazoo, MI 49001.*

*Vetalog, Bristol Myers Squibb for Fort Dodge, Fort Dodge, IA 50501.*