Use of Corticosteroids

C. Wayne McIlwraith, BVSc, PhD, DSc, FRCVS, Diplomate ACVS, ACVSMR

The use of certain intra-articular corticosteroids for equine joint disease are still appropriate but the use of methylprednisolone acetate has deleterious effects on articular cartilage and its use should be questioned. The duration of action of each corticosteroid is still poorly defined and pharmacogenomic methods provide the potential of a more global assessment for pharmacodynamic responses after intra-articular corticosteroid injection. Author’s address: Gail Holmes Equine Orthopaedic Research Center, Colorado State University, College of Veterinary Medicine and Biomedical Sciences, 300 West Drake, Fort Collins, CO 80523; e-mail: Wayne.McIlwraith@colostate.edu. © 2011 AAEP.

1. Introduction
The first report of intra-articular corticosteroids used in the treatment of musculoskeletal conditions in horses and cattle was in 1955.¹ The use has become frequent since that time. Although the use of intra-articular corticosteroids has been cited as harmful in the horse,²,³ more recent research has identified variations in therapeutic effects, with some having beneficial effects and one commonly used product having deleterious effects.⁴–⁶

2. Mechanism of Action
The use of intra-articular corticosteroids for equine joint disease was extensively reviewed in 1996,⁷ and the specific benefits and deleterious side effects of intra-articular corticosteroids in the horse have been clarified more since that time. Corticosteroids are potent anti-inflammatory agents, and they inhibit the inflammatory process at all levels. Although traditional thinking has ascribed corticosteroid anti-inflammatory effects to stabilization of lysosomal membranes with a concomitant release of lysosomal enzymes, the anti-inflammatory effect is now known to be much more complex and far-reaching.⁸ Glucocorticoids exert their effects through cytoplasmic receptors. In addition to the well-known general effect of reducing capillary dilation, margination, migration, and accumulation of inflammatory cells, glucocorticoids inhibit the synthesis and release of several soluble mediators, including acting on the prostaglandin cascade, and they have been shown to inhibit interleukin-1 (IL-1), considered the most important mediator of cartilage degradation and tumor necrosis factor (TNFα) at low concentrations.⁹ Pain relief is attributed to inhibition of prostaglandin synthesis in large measure, specifically by inhibiting the enzyme phospholipase A₂ and cyclooxygenase (COX)-2 expression in the arachidonic cascade.¹⁰

3. Indications
The use of intra-articular corticosteroids is primarily indicated for the treatment of traumatic synovitis and capsulitis.¹¹ Traumatic synovitis and capsulitis are significant because of the direct functional effects, including pain and restrictive function, in the joint as well as the release of deleterious mediators, including IL-1, metalloproteinases, aggrecanases, prostaglandin E₂ (PGE₂), and free
radicals that can lead to degradation of articular cartilage and consequent osteoarthritis (OA).

4. Available Choices

The most commonly used intra-articular corticosteroids are betamethasone acetate–betamethasone sodium phosphate,\textsuperscript{a} triamcinolone acetonide\textsuperscript{b} (TA), methylprednisolone acetate\textsuperscript{c} (MPA), and isoflupredone acetate\textsuperscript{d}. Experimental studies of the three most commonly used intra-articular corticosteroids, namely betamethasone esters, MPA, and TA, have been performed using an osteochondral fragment model of OA developed at Colorado State University (CSU).\textsuperscript{4–6}

The first product studied was betamethasone sodium phosphate–betamethasone acetate\textsuperscript{e}. Osteochondral fragments were created arthroscopically on the distal aspect of both middle carpal joints in 12 horses, and one joint was treated with 2.5 ml betamethasone sodium phosphate–betamethasone acetate at 14 days after surgery, which was repeated in 35 days.\textsuperscript{4} The opposite joint was injected with saline as a control. No deleterious side effects to the articular cartilage (based on histology, histochemistry, and uronic acid content) were shown. In addition, comparison of exercise versus non-exercise on injected joints showed that exercise also did not have any harmful effects in the presence of corticosteroid administration.

In subsequent studies with intra-articular corticosteroids (as well as other treatments), the model was modified so that the opposite joint was not used as a control, and also, the CSU chip fragment model was modified to more effectively produce early OA change. MPA and TA were tested using three groups, and the test system is depicted in Figure 1.\textsuperscript{5,6} Eighteen horses were randomly assigned to each of three groups (six horses per group). Both middle carpal joints in the placebo control group (ST) horses were injected intra-articularly with polyionic fluid. The corticosteroid control group horses (ST CNT) were injected with corticosteroid in the middle carpal joint without an osteochondral fragment, and the opposite middle carpal joint was injected with a similar volume of polyionic fluid. The corticosteroid-treated group horses (ST TX) were treated with corticosteroid in the joint that contained the osteochondral fragment, and the opposite middle carpal joint was injected with a single volume of polyionic fluid. All horses were treated intra-articularly on days 14 and 28 after surgery and exercised on a high-speed treadmill for 6 wk starting on day 15.

In joints containing an osteochondral fragment and treated with MPA, there was reduction, although not a significant one, in the degree of lameness; however, there were significant PGE\textsubscript{2} trends in the synovial fluid and lower scores for intimal hyperplasia and vascularity (no effect on cellular infiltration in the synovial membrane compared with placebo-treated joints).\textsuperscript{6} Of more importance, modified Mankin scores (a score of negative histopathological change in the articular cartilage) were significantly increased in association with MPA, confirming deleterious effects of intra-articular administration of MPA on articular cartilage.\textsuperscript{6} All of these changes were observed at 70 days, which was 42 days after the second and last injection of MPA. It was also noted that synovial aspiration was difficult (low volume and high viscosity) after treatment with MPA, and this was not seen with the other corticosteroids that were tested. In other work, repetitive intra-articular administration of MPA to exercising horses has been shown to alter the mechanical integrity of articular cartilage, but there was no effect on subchondral or cancellous bone.\textsuperscript{12} In an earlier publication investigating joint function and healing after intra-articular administration of 120 mg MPA, it inhibited the development and maturation of repair tissue of surgically created full-

![Figure 1](image-url)
thickness articular cartilage defects in exercised horses at 42 days and incited potential long-term (180 days) detrimental synovial membrane inflammation. However, a single dose of MPA did not cause long-term detrimental effects (180 days) in the quality of the repair tissue (percentage of fibrocartilage).

5. Duration of Action

Duration of action has been poorly defined. In general, betamethasone acetate–betamethasone sodium phosphate has been classified as intermediate to long-acting, TA has been classified as intermediate, MPA has been classified as intermediate to long acting, and isoflupredone acetate has been classified as short to intermediate duration of action.

6. Combined Use of Hyaluronan and TA

There is some support of the combination of TA and hyaluronan (HA) being beneficial from one study of 16 human patients with knee OA. This was a 1-yr, single-blind, randomized study in which 24 patients were treated with intra-articular HA one time per week for 3 wk and then again at 6 mo (total of six injections). Sixteen of these patients also had 1.0 ml triamcinolone before the first and fourth HA injections, and evaluation using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) index (used to assess patients with OA of the hip or knee using 24 parameters, including 5 indices of pain, 2 indices of stiffness, 7 indices of social function, and 10 indices of emotional function) found that the results were better with the combination of these two products. There was no progression of OA on magnetic resonance imaging (MRI) in either group.

There is indirect evidence that the use of HA together with TA should provide clinical benefit in the horse. In a recent study, the use of intra-articular HA as well as intra-articular polysulfated glycosaminoglycan was assessed in the CSU chip fragment model. Intra-articular injection of 20 mg HA was done at 14, 21, and 28 days. There was significantly less cartilage fibrillation with HA at day 70, despite less impressive reduction of synovial effusion and synovial membrane vascularity and subintimal fibrosis compared with polysulfated glycosaminoglycan. The combination of the potent anti-inflammatory corticosteroid TA and the chondroprotective HA is, therefore, logical.

7. 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 a report of no cases of laminitis in 1,200 horses treated when a dose did not exceed 18 mg. 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.

A relatively recent legal case in the United Kingdom where a horse developed laminitis after receiving 80 mg TA in each tarsus and 20 mg dexamethasone into its back led to the development of a review of the literature and a retrospective study of one clinician’s cases. The review of the literature revealed that good evidence linking laminitis to corticosteroid injection was lacking and that a large-scale multicenter trial was needed. 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. For the majority of the time, TA was used, and the upper total dose ranged from 20 to 45 mg.

8. 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. In this study, MPA was administered using two routes, and the effect on mRNA gene expression from muscle cells was monitored over time using microarrays. This work showed the ability of measuring gene expression (either up- or down-regulated) as a pharmacodynamic (pharmacogenomic) method. As expected, a host of genes were differentially expressed (up- or down-regulated) as a consequence of corticosteroid administration. Also, differential gene expression occurred even after the pharmacokinetic effects were gone. This result may explain why exogenous corticosteroids have both acute and chronic effects.

References and Footnotes


*Betavet Soluspan (now available as Celestone Soluspan), Shering-Plough Animal Health Corporation, Union, NJ 07083; Celestone Soluspan, Schering-Plough/Merck. Whitehouse, NJ 08889.

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

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


*Adequan, Luitpold Pharmaceuticals, Inc., Shirley NY 11967.