THE EFFICACY OF SYSTEMICALLY ADMINISTERED ANTI-ARTHRITIC DRUGS IN AN INDUCED EQUINE CARPITIS MODEL

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SUMMARY

The efficacy of two systemically administered drugs for the treatment of equine joint injuries was assessed in a randomized blinded trial using the chemically induced equine carpitis model previously used to determine the dose and efficacy of both products. After a 10–day acclimation period, carpitis was induced by intracarpal injection of Complete Freund’s Adjuvant (CFA) in twenty mature horses free of clinical and radiographic evidence of synovitis or DJD. Five days after model induction, the horses were stratified based on lameness evaluation and randomly assigned to 2 groups of 10 horses each.

Parameters evaluated included lameness score, maximum range of carpal flexion, carpal circumference, stride length, and synovial fluid protein. These parameters were measured prior to model induction, 5 days after model induction (immediately prior to initial treatment) and once weekly for 6 weeks. Radiographs of the carpus were taken prior to model induction and 6 weeks after treatment began. Treatment began 5 days after model induction. One group of 10 horses received 40 mg sodium hyaluronate by intravenous injection weekly for 3 weeks and the other group of 10 horses received intramuscular injections of 500 mg PSGAG every 4 days for 7 treatments.

Both treatment groups showed significant improvement from pretreatment baseline values (based upon percentage recovery to normal pre-model induction values) for lameness score, stride length and maximum carpal flexion (p < 0.05) at each post treatment evaluation. The PSGAG treated group had significant improvement in synovial fluid protein at post treatment weeks 2 and 3. The improvement (percent recovery) in the PSGAG treated group was significantly (p < 0.05) better than that of the intravenous sodium hyaluronate treated group for stride and flexion at post treatment weeks 1 through 6, for lameness score at post treatment weeks 1 through 3 and for carpal circumference at post treatment week 4.

Both intravenous sodium hyaluronate and intramuscular PSGAG induced significant improvement in clinical lameness parameters; intramuscular PSGAG yielded consistently better results in this experimental model.

INTRODUCTION

The medical management of non-septic arthritis and degenerative joint diseases in horses remains a challenge to the equine practitioner. Treatment options have become more diverse in the past 10 years. Traditional medical therapy includes nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular corticosteroids. These treatments control joint inflammation effectively; more recent evidence suggests that certain corticosteroids may actually exert some protective influences on joint tissues.1 Newer intraarticular medications such as sodium hyaluronate (HA) and polysulfated glycosaminoglycan (PSGAG) not only suppress joint inflammation but also improve the synovial fluid environment in injured joints.2 PSGAG has been shown to exert protective effects on potentially damaged equine articular cartilage.3

In the past 5 years, anti-arthritic drugs administered by systemic routes have been introduced and have gained in popularity due to efficacy, ease of administration and reduced risk of post intraarticular injection sepsis. PSGAG administered by the intramuscular route at a dose of 500 mg every 4 days for 7 treatments produced significant improvement in lameness, carpal flexion, carpal circumference, stride length, and synovial fluid protein in a chemically induced equine synovitis model.4 Clinical trials and widespread clinical use have confirmed this efficacy.5 Pharmacokinetics studies have shown the drug to be present in synovial fluid within 2 hours of intramuscular injection and therapeutic levels are maintained in the articular cartilage for at least 96 hours after intramuscular injection.6

Intravenously administered HA was determined to be efficacious in the same chemically induced equine synovitis model. A dose of 40 mg weekly for 3 weeks provided significant (p < 0.05)
improvement of lameness, stride length and range of motion. This efficacy has been confirmed in clinical trials and in routine clinical use. The exact mechanism of distribution of the drug to joint tissues and the mechanism of action is not well understood.

The objective of this study was to compare these 2 systemic treatments in a CFA induced model of equine carpitis.

MATERIALS AND METHODS

Animals
Twenty, mature, grade horses (9 mares and 11 geldings) aged 3-10 years were obtained from a local horse supplier. The horses were dewormed, vaccinated and acclimated to the laboratory environment as per the standard procedures for the laboratory. The horses were fed a maintenance ration of mixed grain with grass hay and water ad lib. The horses were housed in 12’ x 12’ indoor box stalls. Ten days were allowed for acclimation.

Experimental Model
Carpitis was induced in the left radial carpal joint by aseptic injection of the joint with CFA. A period of 5 days was allowed for the carpitis to develop.

Treatments
Drugs for the trial were obtained through an ethical veterinary distributor. Sodium hyaluronate (HAIV) was obtained in 40 mg vials and polysulfated glycosaminoglycan (PSGAG) was obtained in 500 mg vials. All drugs were stored under refrigeration until used. All treatments were administered according to the package insert directions provided by the manufacturers. For HAIV, 40 mg was administered by intravenous injection once weekly for 3 weeks. For PSGAG, 500 mg was administered by intramuscular injection every 4 days for 7 treatments.

Test System
All parameters were measured prior to model induction, 5 days after model induction and prior to initial treatment, and once weekly for 6 weeks after treatment was initiated. Lameness was graded using the following scale:

0 = no lameness at a walk or trot
1 = no lameness at a walk; alteration of gait at a trot
2 = alteration of gait at a walk; head bob at a trot
3 = obvious head bob at a walk or trot
4 = intermittent non-weight bearing
5 = persistent non-weight bearing

Carpal flexion was measured by slowly flexing the left carpus until the horse resisted. The maximum flexion angle was measured in degrees with a large protractor. Carpal circumference was measured in centimeters at the level of the mid accessory carpal bone using a flexible tailor’s tape. Stride length was measured by walking the horse down a raked shed row. The toe-to-toe length of 3 strides of the left forelimb was measured in inches. Samples of synovial fluid were collected from the left radial carpal joint by aseptic arthrocentesis. Samples were placed in EDTA Vacutainer tubes and shipped on ice for determination of synovial fluid protein.

Lateral and lateral to medial oblique radiographs were taken of the left carpus of each horse prior to model induction and 6 weeks after treatment began.

Study Design
This study was performed in 2 replicates of 10 horses each. Baseline measurements were taken in each animal prior to lameness induction and 5 days after model induction (pretreatment). The resulting difference from pre-induction baseline was taken as a measure of severity. With each replicate of 10 horses, 5 pairs with similar levels of severity were identified and treatments assigned randomly to each horse of the pair using a computerized randomization system.

One investigator performed all treatments and the clinician measuring the assessment criteria was blinded to the treatment group assignments.

Humane Considerations
The protocol required that horses suffering from undue pain could be treated with an analgesic drug with no anti-inflammatory activity. Horses were to be dropped from the study and treated for pain under the following conditions:

1. persistent poor appetite (more than 3 consecutive days)
2. failure to maintain body weight
3. persistent grade 4 or 5 lameness (more than 3 consecutive days).

Statistical Analysis
The response variables were analyzed at pretreatment and at post treatment weeks 1-6. Two characteristics were used: the arithmetic differences from pretreatment baseline and percent recovery of the difference between pre-treatment and post treatment baseline (model induced deficit). The statistical analysis consisted of univariate and multivariate analysis of variance. The influence of replicate and pairing were considered but neither proved to be significant and were subsequently dropped from the model. Therefore, the univariate analyses at each week were Student’s t tests of the treatment means. The multivariate analysis at each week provided a simultaneous contrast of the means of the 5 variables (circumference, flexion, lameness, stride and protein) between PSGAG and HAIV using multivariate T² statistics. The average change from baseline and the average patient recovery over the six
observation weeks were analyzed for differences between treatments.

RESULTS

Graphs 1-5 of the raw data means from baseline to six weeks clearly show the effects of the model induction and subsequent treatment for animals under both treatments. With some measures (e.g., stride length) there were slight but insignificant differences between the treatment groups at pre-induction and/or at pretreatment baselines. Adjustment was made for these baseline differences, on a horse-by-horse basis, by simply subtracting the baseline value from scores at later times or by calculating changes in terms of the percent reduction of the induced deficit at pretreatment.

With the exception of carpal circumference and synovial protein these graphs also indicate a tendency of the animals to return toward normal values under both treatments. In fact, the time of maximum effect seems to occur at about 3-4 weeks after treatments are initiated. Conditions deteriorated somewhat on weeks 5 and 6 (after treatment had ceased).

By a comparison of means across time, Graphs 1-5 indicate that under the conditions tested PSGAG treated animals improved more than HAIV treated animals. The following paragraphs detail significant differences in terms of percent recovery from the induced deficit (Table 1). For all the variables except carpal circumference the pattern of significant (p < 0.05) differences between treatments were similar whether expressed as a simple change from baseline or as a percent recovery (Table 2).

Carpal circumference was increased by model induction. The PSGAG group did not change significantly after treatment (Table 1). However, the HAIV group had significant (p<0.05) exacer-

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P-values for PSGAG (1st cell value) and HAIV (2nd cell value)

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+ Significant improvement — Significant worsening
bution of carpal swelling over all times except week 3 (last week of treatment). These differences in response between PSGAG and HAIV were significant at all times when both were expressed as simple changes from baseline but only on week 4 when the responses were expressed as a percentage of the model induced effect (Table 2).

Maximum carpal flexion was reduced by about 60 degrees by model induction. After the first week of treatment, PSGAG treated animals recovered an average of 34% (p = 0.00004) of the model induced deficit (Table 1). HAIV treated animals had a significant (p = 0.03) 13% recovery. This was significantly (p = 0.006) less than the PSGAG treated animals (Table 2). This pattern continued throughout all subsequent weeks, with both treatments showing significant (p < 0.02) percent recovery from pretreatment deficits (Table 1) but with the PSGAG treated group averaging significantly (p < 0.03) better improvement than that for the HAIV group (Table 2). The mean percent recovery over all weeks was 53% for PSGAG treated horses compared to 23% for the HAIV horses (p = 0.003; Table 2).

The lameness scores averaged about 3 after model induction. Animals treated with both PSGAG and HAIV improved over time with significant (p < 0.03) percent recoveries at each observation period (Table 1). The PSGAG group was significantly (p < 0.006) better than the HAIV group over the first 3 weeks (Table 2). Average improvement over all weeks was 63% and 41% for PSGAG and HAIV treated horses, respectively (p = 0.01; Table 2).

Stride length was markedly reduced by model induction. Both the PSGAG and HAIV treated animals made rapid improvements with highly significant (p < 0.0006) percent recoveries at each week (Table 1). Again the PSGAG treated horses demonstrated significantly (p < 0.005) greater benefit than the HAIV treated horses at each week (Table 2). The average percent recovery over all weeks was 93% for PSGAG treated horses and 56% for HAIV treated horses (p = 0.0002; Table 2).

Synovial fluid protein was increased by model induction and slight improvement was seen with either treatment. Table 1 indicates some improvement in the PSGAG treated horses on week 2 (29% recovery; p = 0.007) and week 3 (20% recovery; p = 0.03) but no significant differences between the HAIV and PSGAG treated horses (Table 2) could be established at any time.

While some individual HAIV treated horses fared as well or better than the PSGAG treated horses, overall odds are that a PSGAG treated horse will show greater improvement than an HAIV treated horse. In fact, when horses are ranked according to their average recovery over all weeks and analyzed using the Mann-Whitney U-test, the odds consistently favor PSGAG treated

Table 2. P-values for comparing PSGAG to HAIV

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+PSGAG significantly better than HAIV (p < 0.05)
horses relative to the HAIV treated horses. The respective odds are 4.7 to 1 with respect to lameness score (p = 0.014), 6.7 to 1 for carpal flexion (p = 0.005) and 24 to 1 for stride length (p = 0.0005). For circumference and synovial protein odds favored neither product.

**DISCUSSION**

Clinically relevant disease models of arthritis and equine degenerative joint disease (DJD) are advantageous in the study of the treatment of the disease. In controlled clinical field trials of equine DJD it is difficult to obtain adequate patient numbers for negative or placebo controlled trials using performance or race horses. Owner acceptability and the humane aspects of requiring athletic horses with DJD to compete without treatment are often unacceptable. The number of patients required to satisfy statistical needs usually requires multiple study centers with the potential of additional variability due to differences between investigators in interpretation of subjective and semi-objective parameters and local variations in training and performance. Controlled studies comparing one or more effective treatments for equine DJD are even more demanding and frequently require 200 or more cases to obtain statistical significance. Under such circumstances such trials may be impractical and/or cost prohibitive.

A consistent disease model with clinically relevant, semi-objective response parameters offers real advantages for determining the efficacy and optimal dose regimen of drugs used to treat equine DJD. Strong statistical findings are possible with greatly decreased numbers of animals. Although no animal model of DJD will be identical to the clinical disease, provision of consistent results approximating those of clinical disease permit less demanding confirmatory clinical trials.

The CFA carpitis model has been used successfully for many years to establish the optimal dose and efficacy and/or to confirm the efficacy of many of the drugs currently used to treat equine DJD. The efficacy and optimal dose of intraarticular PSGAG, intraarticular HA, intravenous HA, and several nonsteroidal anti-inflammatory drugs used to treat equine DJD have been established using the CFA carpitis model. The dose and efficacy of all these drugs have been confirmed in subsequent clinical trials and in routine clinical use. In all cases the dose and efficacy established by statistically significant findings in this model have been consistent with results obtained by trials in clinical cases of equine DJD. Thus much of the current basis for the medical management of equine DJD has been dependent on findings in this disease model which produces a consistent repeatable syndrome with subjective and semi-objective clinically relevant lameness parameters.

The model has been criticized for being excessively inflammatory. The model does create a significant synovitis and, untreated, radiographic evidence of DJD in 3-4 weeks. Horses subjected to the model consistently remain on feed and even untreated animals will continue to maintain body weight or even gain weight. In our facility the horses are carefully monitored and animals that have a lameness score of greater than 3 for 3 consecutive days, that do not clean up feed for more than 3 consecutive days, or that exhibit any distress due to pain are medicated with a nonanti-inflammatory analgesic drug or removed from the trial and treated. In the past 2 years we have performed 3 trials using the CFA model in 53 horses. Only 2 horses (3.8%) have required medication for pain and/or removal from the trial for humane reasons.

Clinically, equine DJD is often the result of a cascade of pathological events secondary to synovitis and capsulitis due to the repetitive trauma encountered in athletic training and performance. Inflammogens and catabolic enzymes released from invading leukocytes and local joint tissues lead to destruction of synovial fluid hyaluronate and catabolic changes in the articular cartilage. The ultimate effect of progressive unresolved synovitis is articular cartilage degeneration, fibrosis of the joint capsule (loss of normal range of motion), osteophyte formation and loss of joint space.

The CFA carpitis model produces a comparable clinical syndrome of synovitis, capsulitis, elevated synovial fluid protein, articular cartilage degeneration, and radiographic evidence of DJD (osteophytes). These changes occur over a uniform period of time providing an opportunity to evaluate the effects of medical intervention in a systematic and objective manner with a minimal number of animals necessary to achieve statistical significance.

The intraarticular use of sodium hyaluronate (HA) for synovial inflammation is well established and widely practiced. Although the exact mechanism of action of intraarticular HA remains unclear, clinical anti-inflammatory benefits of this therapy are obvious. HA has both mechanical and cell interaction effects upon inflammation. The entangled coils of HA form a gel-like barrier which limits or regulates movement of large molecules; a filtering function related to concentration and molecular size of the HA molecule. HA also inhibits cell functions such as locomotion, chemotaxis, and cell migration at the site of inflammation. HAIV was recently approved for use in indications similar to intraarticular HA. Efficacy similar to intraarticular HA has been shown in a dose response study using the CFA carpitis model and in clinical trials. Clinical use seemed to confirm this efficacy and HAIV has become an established therapy for equine synovitis.
In an objective study using a carpal chip model with exercise, the anti-inflammatory benefits of HAIV, specifically a significant reduction in synovial fluid concentrations of prostaglandin E2, were confirmed. Also a trend toward decreased GAG synthesis in the cartilage of these horses was noted but the significance of this remains unclear. The mechanism of action of HAIV is unknown; it has been proposed that circulating HA in contact with the cell membrane may induce responses in receptors on the synoviocytes.

In this study HAIV provided rapid and significant improvement in lameness score, stride length and carpal flexion. These results are consistent with previous studies of HAIV in the CFA carpitis model and with previous clinical trials. In this model, HAIV treatment tended to reduce synovial fluid protein during the treatment period (approximately 18% at week 3 versus pretreatment) but the reduction was not statistically significant. In the exercise/carpal chip model study, HAIV treatment also reduced synovial protein levels by approximately 20%. Carpal circumference in this study was relatively unaffected by HAIV treatment; the carpal circumference was actually significantly worsened at weeks 1 and 2 and 4 through 6. In previous studies using this model, HAIV induced little improvement in carpal circumference in weeks 1–4 after treatment was initiated and a slight improvement at weeks 4–6.

The efficacy of intramuscular treatment of equine synovitis and DJD with PSGAG is well established and the drug is widely used in equine practice. PSGAG has been shown to have inhibitory effects on important catabolic enzymes in equine joint tissue, as well as positive effects on synovial fluid protein and hyaluronate concentrations. Positive effects on cartilage metabolism have also been demonstrated including a decrease in the net loss of matrix GAG and collagen characteristically seen in equine DJD. Several anti-inflammatory actions have been demonstrated for PSGAG including inhibition of the synthesis of prostaglandin E2 and inhibition of the complement cascade. The dose and efficacy of intramuscular PSGAG was established in the CFA carpitis model and confirmed in clinical trials in horses with carpal injuries in which intramuscular treatment was shown to be clinically and statistically indistinguishable from intraarticular PSGAG treatment.

In this study PSGAG induced rapid, significant improvements in lameness score, carpal flexion and stride length. These results are consistent with previous studies of PSGAG in the CFA model. In addition PSGAG treatment resulted in a consistent improvement in synovial fluid protein (approximately 30% and 21% at weeks 2 and 3, respectively). This was statistically significant at treatment weeks 2 and 3. In previous studies in this model the significant reduction in synovial fluid protein was more apparent and noted until 2 weeks post treatment. Carpal circumference was not significantly improved or worsened in this trial. In previous trials in this model, carpal circumference was significantly reduced by intramuscular PSGAG treatment.

Comparison of the 2 treatments revealed significant differences in degree of response. The mean percent recovery for each variable is shown in Table 3. The trends toward greater recovery in the PSGAG versus the HAIV treated group is clearly evident.

When the individual horses’ recoveries were ranked over all weeks and analyzed by the Mann-Whitney U-test, the odds favor a significantly better recovery for PSGAG treatment with respect to lameness score (p = 0.014), carpal flexion (p = 0.005) and stride length (p = 0.0005).

We conclude that both treatment with intramuscular PSGAG or HAIV in the CFA carpitis model provided significant improvement in the functional variables of lameness score, carpal flexion and stride length and that PSGAG induced significantly better recovery in these variables. There was a trend toward improved recovery in the PSGAG treated group for carpal circumference and synovial protein but this was not statistically significant except for circumference at week 4 (p < 0.05). In this trial there was significant benefit for the use of PSGAG over HAIV.

### REFERENCES

7. Freedom of Information Summary NADA # 140-863 Legend Injectable Solution (Mobay).

### Table 3. Summary of mean percent recovery for each variable

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**BOOKS AVAILABLE FROM VETERINARY DATA**


**Equine Surgery.** (1992) Jorg A. Auer (Ed) The latest, most complete text on the subject. 90 contributors. 1214 pgs. W. B. Saunders ($125.00 overseas)

**Imprint of the Newborn Foal.** Robert M. Miller, DVM. A swift, effective method for permanently shaping a horse's lifetime behavior. 144 pgs. ($23.00 overseas)

**Equine Reproduction** (1992) Angus McKinnon & James Voss Ed. By Norman Rantanen and Michael Hauser. Includes all papers presented on tendon, ligament and soft tissue injuries; 430 pages. Edited by Norman Rantanen and Michael Hauser. Includes all papers presented on tendon, ligament and soft tissue injuries; 430 pages. ($130.00 overseas)

**Equine Sports Medicine** (1989) William E. Jones (Ed) A complete coverage of the subject, 30 contributors. ($110.00 overseas)

**Veterinary Acupuncture: Ancient Art to Modern Medicine** (1994): Edited by Allen M. Schoen, DVM, MS. Offers veterinarians and veterinary students an introduction to veterinary acupuncture. Mosby. ($110.00 overseas)

**Equine Clinical Nutrition.** (1995) Lon D. Lewis An extensively reference, the most complete anywhere. Williams & Wilkins. ($130.00 overseas)

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