Safety Evaluation of Polyglycan™ in Horses.

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Introduction

The normal biomechanical and physiological function of synovial structures are crucial for the horse to be able to perform athletically at its optimal potential. Synovial structures include the diarthrodial joints and tendon sheaths/bursae that collectively function to allow fluid motion of the appendicular skeleton of the horse. When pathological conditions arise that involve these tissues, traditional medical or surgical intervention is commonly indicated. The ultimate goal is the resolution of pain and restoration of normal function so that the horse may return to its previous level of performance.

Hyaluronan (HA or hyaluronic acid) is a normal constituent of synovial fluid found in joints, tendon sheaths, and bursae, and within the extracellular matrix of articular cartilage. HA secreted by the synovium contributes to the viscosity of synovial fluid and is additionally believed to have local anti-inflammatory effects such as the reduction of cytokine expression and inhibition of prostaglandin synthesis and release by macrophages[1]. Intravenously administered sodium hyaluronate has been shown experimentally to improve clinical lameness, synovial membrane histology, and synovial fluid characteristics in an equine carpus osteoarthritis model[2]. Intraarticular and intravenous administration of HA for the treatment of synovitis and osteoarthritis in horses has become commonplace in the practice of equine veterinary medicine.

Polysulfated glycosaminoglycans (PSGAGs) are an important component of the extracellular matrix of articular cartilage. Exogenously administered PSGAGs have been used in many species for their chondroprotective effects, ability to increase HA concentrations in synovial fluid, stimulate cartilage matrix synthesis, and decrease matrix degradation[1]. Chondroitin sulfate is a glycosaminoglycan that is a vital part of aggrecan, a molecule that makes up a large portion of the extracellular matrix of cartilage and imparts compressive stiffness. Glucosamine is an aminomonosaccharide and is further a precursor to the dissacharides found in aggrecan. Chondroitin sulfate and glucosamine are therefore commonly referred to as “building blocks” and are routinely administered parenterally or orally for their ability to stimulate proteoglycan synthesis and inhibit cartilage degradation. In a rabbit model of osteoarthritis a combination of chondroitin

sulfate and glucosamine were more efficacious in retarding the progression of articular cartilage lesions than either agent alone suggesting a synergistic effect[3]. The investigators were also able to demonstrate that a combination of chondroitin sulfate and glucosamine stimulated glycosaminoglycan synthesis by chondrocytes in vitro.

The rationale for the delivery of these products locally into the synovial space are to moderate the local inflammatory processes, provide the "building blocks" necessary for cartilage repair and joint restitution, and protect the joint from further damage. Additionally, the parenteral administration may be efficacious in maintaining normal synovial space homeostasis in performance horses.

Polyglycan™ is a commercially available solution of hyaluronic acid sodium, sodium chondroitin sulfate and N-acetyl-D-glucosamine used for post-surgical lavage of synovial compartments in horses. Independently, sodium hyaluronate has been intravenously administered, polysulfated glycosaminoglycans have been intramuscularly administered and both have been directly injected into joints of horses. The targeted result of exogenous administration of these compounds is reduction of inflammation and preservation/protection of the structural anatomy of joints and tendon sheaths. Protracted elevation of hyaluronan, which can lengthen therapeutic results, has been obtained and determined to be safe after intravenous administration of sodium hyaluronate and intramuscular administration of polysulfated glycosaminoglycans. The purpose of this study is to demonstrate that Polyglycan™ can safely be administered to horses intravenously and intramuscularly. Based upon the long history of the administration of hyaluronic acid, chondroitin sulfate, and glucosamine by a variety of methods it appears reasonable that the intravenous and intramuscular administration of a combination of these compounds should be safe and efficacious for horses.

Material and Methods

All procedures were approved by the institutional animal care and use committee. Six adult horses used for this study. Each horse was determined to be healthy as determined by routine physical examination. All horses were current on vaccinations and deworming status. They were maintained on a diet meeting NRC requirements. No medications had been administered within 8 weeks of initiation of each study protocol. Horses were housed in hospital stalls during the duration of the study period. Baseline evaluation for each horse consisted of physical examination including temperature, heart and respiratory rates, evaluation of skin texture and surface, and evaluation of oral mucous membranes (color, texture, capillary refill time). Any pre-existing sweat patterns or skin reactions were noted and recorded. Complete blood count (CBC) including packed cell volume (PCV), total protein (TP) and blood chemistry profile were obtained at the initiation of the study.

Intravenous administration protocol:

On day one 10 milliliters of Polyglycan™ was administered to each horse into the left jugular vein at a mid-cervical site with an 18 gauge hypodermic needle and 12 ml syringe. This administration was repeated on Days 2, 7 and 8. Cardiac auscultation was performed during each administration. Physical examination parameters as described for

baseline evaluation were recorded at: 10, 30, 60, and 90 minutes, 3, 6, 12, and 24 hours following each administration. All other physical examination parameters were recorded at: 3, 4, 5, 6, 10, and 14 days. CBC and blood chemistry was repeated on days 7 and 14. A 6 week wash out period was provided between intravenous and intramuscular administration protocols.

Intramuscular administration protocol:

On day one 10 milliliters of Polyglycan™ was administered into the left mid-cervical musculature of each horse with an 18 gauge hypodermic needle and 12 ml syringe. This was repeated on Days 2, 7 and 8. Physical examination parameters were monitored as for the intravenous protocol.

The bloodwork and physical examination data for each horse was evaluated from each horse and compared to all others.

Results

Intravenous administration of Polyglycan™:

All horses tolerated the intravenous administration of Polyglycan™. One horse exhibited focal mild hives over the shoulder region 30 minuted following administration on day 8. The reaction improved by 3 hours and had completely resolved by 24 hours post-adminstration. No other abnormalities were observed in any other horses. All horses had normal vital parameters and no abnormalities were observed on CBC and chemistry compared to baseline throughout the duration of the study protocol.

Intramuscular administration of Polyglycan™:

All horses tolerated the intramuscular administration of Polyglycan™. One horse exhibited mild discomfort during intramuscular administration. No other abnormalities were observed in any other horses. All horses had normal vital parameters and no abnormalities were observed on CBC and chemistry compared to baseline throughout the duration of the study protocol.

Discussion

In this study a higher volume of Polyglycan™ and increased dosing interval was utilized than would be routinely prescribed in practice. This was performed in order to demonstrate a margin of safety and evaluate any potential anaphylactic reactions. It could not be determined if the reactor in the intravenous administration protocol on day 8 was related to the Polyglycan™ administration, environmental contact, or other causes. No reaction was observed from the same horse during the intramuscular protocol suggesting that the reaction could have been initiated from another source.

Polyglycan™ is a highly viscous solution which could explain the discomfort observed following the intramuscular administration in one horse. A higher volume (double dose) was also used in this study than would commonly be prescribed. The slow intramuscular administration of Polyglycan™ was well tolerated by the horse during

subsequent administrations. Based upon the results from this evaluation it appears that Polyglycan™ can be safely administered both intravenously and intramuscularly to horses.

References

1. Fortier, LA. Systemic therapy for joint disease in horses. Vet Clin Equine 2005;21(3):547-557.

2. Kawcak, CE, Frisbie, DD, Trotter, GW, et al. Effects of intravenous administration of sodium hyaluronate on carpal joint in exercising horses after arthroscopic surgery and osteochondral fragmentation. Am J Vet Res 1997;58:1132-1140.

3. Lippiello, L, Woodward, J, Karpman, R, et al. In vivo chondroprotection and metabolic synergy of glucosamine and chondroitin sulfate. Clin Orthop 2000;Dec(381):229-240.