

Review of Glucosamine-Containing Oral Joint Supplements: Are They Effective in the Horse?

Stacey L. Oke, DVM, MSc; and J. Scott Weese, DVM, DVSc, Diplomate ACVIM

While glucosamine supplementation is very common and a multitude of commercial products are available, there is currently limited information available to assist the equine practitioner in deciding when and how to use these products. Low bioavailability of orally administered glucosamine, poor product quality, low recommended doses, and a lack of scientific evidence showing efficacy of popular oral joint supplements are major concerns. Authors' addresses: Rolling Thunder Veterinary Services, 225 Roxbury Road, Garden City, NY 11530 (Oke); Ontario Veterinary College, Department of Clinical Studies, University of Guelph, Guelph, Ontario, Canada N1G 2W1 (Weese); e-mail: rollingthunder@optonline.net (Oke). © 2006 AAEP.

1. Introduction

Musculoskeletal diseases are one of the most important causes of morbidity in horses of all types. Osteoarthritis (OA) is of particular concern because of the incidence of disease and the associated effects on performance, usefulness, and life.¹⁻³ To date, there is no cure for OA, and supportive therapy, including non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, is the most common approach taken in the management of this condition.⁴ Anti-inflammatory therapy is not able to stop or slow the progression of the disease, however, and treatment can be associated with significant adverse effects.⁵ As a result, alternative therapies are being used increasingly in both human and veterinary medicine. One of the most common alternative approaches is the oral administration of glucosamine.

The manufacture and sale of equine nutraceuticals, particularly glucosamine containing oral joint supplements (OJSs), is a large and rapidly growing industry. Despite their widespread use, there is

only limited and conflicting information regarding the effect of glucosamine on OA in the horse. Furthermore, poor product quality has been identified in glucosamine-containing OJSs,⁶ and the bioavailability of glucosamine is reportedly very low.^{7,8} Therefore, veterinarians need to question whether glucosamine is capable of playing any role in equine OA.

The goal of this discussion is to review current information regarding the chemistry and pharmacokinetics of glucosamine, results of clinical trials that include glucosamine-containing OJSs and proposed mechanisms of action of glucosamine. Specific products that meet label claims (in terms of glucosamine content) can be identified on request. The information presented here will enable veterinarians to counsel their clients regarding the potential risks and benefits of nutraceuticals currently marketed to treat equine OA.

2. OA in the Horse

OA, previously referred to as degenerative joint disease, can be defined as a group of disorders affecting

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diarthrodial joints characterized by alterations in articular cartilage metabolism, leading to a physical degeneration of the cartilage, accompanied by changes in the bone and soft tissues of the joint.^{2,4,9-11,a} As has been described in detail elsewhere,¹² articular cartilage is comprised of a sparse population of cells within a large extracellular matrix composed of dense collagen fibers, a high concentration of proteoglycans and a smaller concentration of other proteins. Articular cartilage is continuously being turned over and a delicate balance between catabolism and anabolism exists. Any factor or event (e.g., trauma, release of cytokines, and inflammatory mediators) that disrupts this balance results in degradation of articular cartilage by such enzymes as matrix metalloproteinases (MMPs) including collagenase, stromelysin, and aggrecanase.^{4,13}

3. Medical Therapy

Because there is no cure for OA, the goal of pharmacological management is to control the clinical signs of the disease, minimize pain, and improve mobility.¹⁴ Ideally, OA therapy would also slow or arrest the progression of disease.¹⁵ In the equine patient, the administration of NSAIDs and intra-articular corticosteroid therapy are most commonly used to treat OA.^{4,16,17} There is some evidence, however, that NSAIDs and corticosteroids may have potentially negative effects on articular cartilage metabolism¹⁶ (although this contention has neither been proven nor is it universally accepted). Regardless, because some adverse reactions associated with NSAIDs and corticosteroid administration are also of concern, horse owners and health practitioners are actively seeking alternate therapies for OA.⁵

4. The Nutraceutical Industry

The nutraceutical industry has grown remarkably over the past decade.^{18,19} Nutraceutical sales of glucosamine and chondroitin sulfate designated for human consumption presently exceed \$600 million annually,²⁰ and the veterinary industry alone is responsible for sales currently in excess of 50 million dollars annually.^{15,18}

Definition

According to the U.S. Food and Drug Administration (FDA), the term nutraceutical refers to compounds taken orally that are neither nutrients nor pharmaceuticals. The nutraceutical family of products currently encompasses a broad and varied list of substances including dietary supplements, functional foods, and genetically engineered foods, among others. Nutraceutical substances are not required to have undergone any pre-market approval process, provided they do not claim to treat, cure, or mitigate disease.^{15,18}

Regulation

In many countries, veterinary nutraceuticals are regulated differently than nutraceuticals destined

for human consumption. In the United States, the Center of Veterinary Medicine (CVM), formed by the FDA in 1962, is responsible for ensuring human safety of drugs used in animals. The CVM has determined that the 1994 Dietary Supplement Health and Education Act (DSHEA) applies only to human nutraceutical products. Despite the existence of the CVM, the American Association of Feed Control Officials (AAFCO) was organized in response to the confusion regarding the regulation of veterinary nutraceuticals. This non-regulatory group's goal is to ensure animal feeds, including nutraceuticals, are safe, effective, and useful. Other non-regulatory interest groups also exist to help promote quality, safety, and long-term effectiveness of nutraceuticals used in veterinary medicine such as the National Animal Supplement Council.^{15,18}

Ultimately, the FDA is responsible for regulating veterinary nutraceuticals in the United States. The FDA views veterinary nutraceuticals as unapproved drugs if their use is intended as a drug (which they commonly are). Unsafe nutraceuticals or products sold with a label claim or advertised with a claim indicating use for the treatment or prevention of disease or the ability to alter body structure and function falls under FDA jurisdiction. The FDA may therefore take regulatory action against the manufacturers of such products. In reality, a multitude of veterinary nutraceuticals are sold with unproven label claims and advertised with medical claims. The FDA, however, prioritizes regulatory issues and veterinary nutraceuticals do not typically rate very high on the FDA's priority list.^{15,18} Enforcement of current regulations is therefore extremely lax.

In addition to the confusing regulation of veterinary nutraceuticals and the FDA's choice to overlook labeling violations in nutraceutical products marketed for animal use, there is no requirement for nutraceutical manufacturers to prove safety or efficacy of their products. Furthermore, there is no requirement of current good manufacturing practices (cGMPs) for manufacturers to guarantee high-quality products or batch-to-batch consistency.^{15,18}

Quality

Likely as a result of lax regulation, a variety of studies have identified poor quality in nutraceutical products used to treat OA.²¹⁻²³ Various groups have evaluated the content of glucosamine-containing OJSs including Russell et al.,²⁴ who found only 2 of 14 commercial over-the-counter human glucosamine sulfate products actually contained the amount of product listed on the label. In a similar study, Oke et al.⁶ reported that 9 of 23 equine OJS products contained less glucosamine than claimed by the manufacturer. Of these, four products contained <30% of the expected amount of glucosamine.

In response to the identification of poor product quality, veterinarians are being encouraged to familiarize themselves with a number of nutraceuticals used in horses, especially if practitioners are recommending OJSs to their clients.^{16,19} In addition to the philosophy of “you get what you pay for,” nutraceutical consumers have been encouraged to buy the most expensive products as they are likely to have information regarding quality, efficacy and safety readily available.^{15,18} Oke and Weese, however, identified no correlation between product quality and price of equine OJSs.^b Furthermore, Oke and Weese⁶ identified a number of companies with a poor quality product claiming to have scientific studies supporting their product.^b This emphasizes another concern with the nutraceutical industry, whereby product manufacturers claim to have scientific evidence to support their product, yet scrutiny of these studies indicates poorly designed studies or anecdotal reports that are not published in any form of peer-reviewed literature.

5. Oral Joint Supplements in Horses

Oral joint supplements currently marketed to the equine patient typically include, alone or in combination, glucosamine, chondroitin sulfate, hyaluronic acid, methylsulphonylmethane, vitamins, or herbal products such as yucca, devil's claw, or grapeseed extract.⁶ Glucosamine is an essential component of normal, healthy articular cartilage, and it is possible, therefore, that when administered it may have a beneficial effect in OA.⁶

In addition to the number of products containing low levels of glucosamine, equine OJSs have also been found to recommend subtherapeutic doses of glucosamine.⁶ The current recommended dosage is 20 mg/kg or 10 g orally per day in an average 500-kg horse.^{8,13} Products containing low levels of glucosamine and/or recommending subtherapeutic doses are unlikely to be effective, are an unnecessary expense, and may delay the use of other, potentially beneficial treatments.

6. Glucosamine

Chemistry

Glucosamine is a water soluble amino monosaccharide (2-amino-2-deoxy- α -D-glucose) with a molecular weight of 179 and a pKa of 6.91 at 37°C. After oral administration of glucosamine (either glucosamine HCl or glucosamine sulfate), there is dissolution of the salts to generate the active ingredient, glucosamine free base (GFB).¹³

Safety

Glucosamine (either as a sulfate, hydrochloride or *N*-acetylglucosamine) is widely regarded as safe. No LD₅₀ has been established as no mortality in mice or rats is observed after administration of very high doses (5000 mg/kg orally).²⁵ Typical side effects reported in humans include increased blood

pressure, diarrhea, fatigue, abdominal pain, headache, dyspepsia, cardiac failure, allergic episode, and neuritis, among others.¹⁴ There do not seem to be any studies reporting adverse effects associated with glucosamine therapy in animals, including the horse.

Bioavailability

Almost complete bioavailability of glucosamine has been shown in rats, dogs, and humans.²⁶⁻²⁸ Newer studies using high-performance liquid chromatography (HPLC) techniques, rather than radioisotope assays, have found that glucosamine has only a 21% and 12% bioavailability in humans and dogs, respectively.^{21,29}

Within the past 2 years, two independent research groups each showed that the bioavailability of orally administered glucosamine in the horse is <6% using non-radioisotope assays.^{7,8} Of that, synovial fluid glucosamine levels are <10% of serum glucosamine levels, indicating that glucosamine does not readily diffuse from the circulation into synovial fluid.⁸ In addition, synovial fluid glucosamine levels remain measurable when serum glucosamine levels are no longer detectable, suggesting that glucosamine in the synovial fluid is not used by the cartilage as substrates for glycosaminoglycans.⁸ Indeed, the inefficient use of glucosamine by cells in the intra-articular joint tissues has been reported.^{30,31} Moreover, Mroz and Silbert³² concluded that chondrocytes have the capacity to form glucosamine from glucose in excess of the amounts provided from exogenous sources unless very high concentrations (that could not be achieved through oral administration) of glucosamine are used.

7. Clinical Trials

Only a select few equine researchers have attempted to evaluate glucosamine-containing OJSs in vivo. In a non-peer-reviewed report, White et al.³³ evaluated the effect of a glucosamine-containing OJS in horses free of clinical and radiographic evidence of joint disease. After inducing a synovitis, no improvement in lameness score, stride length, carpal circumference, maximum carpal flexion, or synovial fluid protein were noted compared with control animals. This study concluded that the OJS in question had no anti-inflammatory or chondroprotective activity at the dose or treatment regimen recommended by the manufacturer. Unlike the previous study, Hanson et al.³⁴ evaluated 25 horses diagnosed with joint disease and found a significant improvement of the horses treated with a glucosamine-containing OJS in terms of lameness grade, flexion test grade, and stride length. The value of both studies, however, is questionable because of the small sample sizes used by both groups and the lack of a control or placebo group and subtherapeutic doses of glucosamine used in the study of Hanson et al.

In human medicine, a plethora of *in vivo* studies evaluating the effectiveness of orally administered glucosamine have been performed. One of the landmark clinical studies evaluating glucosamine in human patients was performed by Reginster et al.¹⁴ This study was a randomized double-blind placebo-controlled trial to determine if glucosamine sulfate had any effect on the progression of symptoms and joint structure changes in 212 patients with OA. This 3-yr study found no significant joint space narrowing in patients receiving glucosamine sulfate, and WOMAC scores (Western Ontario and McMaster Universities osteoarthritis index for scoring symptoms) worsened slightly in patients receiving placebo compared with the patients treated with glucosamine sulfate. This study concluded that glucosamine could be a disease-modifying agent in OA.

Two meta-analyses also are worth mentioning here. First, Towheed et al.³⁵ evaluated 16 randomized controlled trials evaluating glucosamine therapy in humans. In the 13 trials that compared glucosamine to a placebo, glucosamine was found to be superior in all but one trial. In the four trials that compared glucosamine to an NSAID, glucosamine was superior in two trials and equivalent in the remaining two. Second, McAlindon et al.³⁶ performed a meta-analysis of 15 double-blind randomized placebo-controlled clinical trials in human hip and knee OA. This group concluded that OA trials collectively show moderate to large effects on OA symptoms but because of methodological insufficiencies identified by McAlindon et al., the efficacy of glucosamine and chondroitin sulfate are likely to be more modest than the individual studies report. McAlindon et al. did concede, however, that even modest efficacy may play an important role in clinical OA considering the safety of orally administered glucosamine.

Despite the myriad of clinical studies reporting favorable results for glucosamine, support for glucosamine (as either a symptomatic or disease-modifying drug of OA) is not universal. Most notably, the results of the GAIT study were published in the *New England Journal of Medicine* in March 2006.³⁷ This was a multicenter, double-blind, placebo- and celecoxib-controlled glucosamine/chondroitin Arthritis Intervention Trial that spanned 24 weeks and enrolled 1588 subjects. This study concluded that glucosamine did not reduce pain effectively in the overall group of patients with knee OA.

In general, problems with *in vivo* studies are numerous, thereby casting further doubt regarding the effectiveness of orally administered glucosamine products. The major criticisms of *in vivo* studies include the fact that many studies are funded by the manufacturers of nutraceutical compounds, small population sizes are used with poor follow-up, and methodological flaws.^{36,38-40} Interestingly, it has been reported that glucosamine has shown moderate efficacy in meta-analysis and industry sponsored

trials, whereas non-industry sponsored trials did not show a significant benefit.⁴¹

8. Proposed Mechanisms of Action of Glucosamine in OA

The Precursor Supply Theory is the most popular explanation regarding the apparent beneficial effects of glucosamine in OA. This theory states that glucosamine supplies excess basic building blocks for the synthesis of cartilage glycosaminoglycans^{5,8,42} and/or bypasses rate-limiting steps in glycosaminoglycan synthesis.^{5,15}

Interestingly, it has been counter-suggested that it is simply the sulfate moiety of glucosamine sulfate that mediates clinical benefit and not the glucosamine itself. This is clinically relevant because it predicts that the non-sulfated salts of glucosamine (i.e., glucosamine hydrochloride and *N*-acetyl glucosamine) will be ineffective.⁴³

As a result of extensive *in vitro* testing, it is postulated that one or more alternate mechanisms of action for glucosamine in OA may include:

- Squelching small signaling molecules such as NO and oxygen radicals that can damage articular cartilage.^{5,44}
- Exerting anti-inflammatory properties by decreasing prostaglandin E₂ (PGE₂) levels through suppression of cyclo-oxygenase-2 (COX-2) gene transcription¹⁶ or by increasing the production of hyaluronic acid in synovial fluid.⁵
- Mediating aggrecanase degradation of articular cartilage.⁵
- Exerting anticatabolic effects by decreasing expression, synthesis, or activity of matrix metalloproteinases (MMPs).¹⁵

Since the exact mechanism(s) of glucosamine on cartilage metabolism remain to be elucidated⁴⁵ and because high *in vitro* doses are being used to study glucosamine,^{8,15} extrapolation of findings to the *in vivo* setting must be done with caution.

9. Conclusion

Drugs for the treatment of OA belong in one of two categories: symptom-modifying drugs of OA and structure-modifying drugs if they are able to interfere with the progression of disease.¹⁴ To date, no drugs can be included in the latter category despite aggressive research efforts in both human and veterinary medicine. Glucosamine, however, continues to be evaluated and aspires to be the first compound identified as a structure-modifying drug for OA. Despite the very low bioavailability of orally administered glucosamine in the horse, poor product quality, and the lack of shown efficacy, glucosamine-containing OJSS are widely used by horse owners, trainers and veterinarians alike. Equine practitioners are encouraged to familiarize themselves with nutraceutical products with proven qual-

ity (please contact the author for more information) and to recommend therapeutic dosages (i.e. 10 g glucosamine orally per day) by carefully reading the label guidelines and ingredients. Furthermore, equine practitioners and consumers should press manufacturers and distributors of glucosamine products to show safety, quality, and efficacy of their products in properly designed and executed clinical trials.

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