Review of the Potential Indications and Contraindications for Equine Oral Joint Health Supplements

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Despite the widespread use of oral joint health supplements in the equine practice, there is limited evidence-based information describing either the appropriate or optimal use of these products. This review critically examines the current literature and identifies potential indications, contraindications, and dosing recommendations. Authors’ addresses: Rolling Thunder Scientific, 34 Lasby Lane, Acton, Ontario L7J 2W9, Canada (Oke); and Equine Orthopaedic Research Laboratory, Colorado State University, Fort Collins, CO 80523 (McIlwraith); e-mail: Wayne.McIlwraith@colostate.edu. © 2008 AAEP. *Presenting author.

1. Introduction

Over the past decade, oral joint health supplements (OJHSs) have become a mainstay in the equine industry and are among the most popular type of nutritional supplement.1 Market surveillance reports indicate that equine products alone are responsible for at least $50 million in annual sales and that the sale of all veterinary supplements, including equine OJHSs, are anticipated to continue to grow at a near exponential rate until at least 2009.1–3 OJHSs are economical compared with the IV administration of non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular administration of corticosteroids or other pharmaceutical drugs. Additionally, OJHSs are widely perceived as both safe and efficacious by consumers. In contrast, adverse events are associated with NSAID and corticosteroid administration, and potentially detrimental effects of these agents on articular cartilage metabolism (as described by Goodrich and Nixon4) have been reported.

Problems surrounding the use of OJHSs include the lack of government regulation and the resultant widespread availability of poor quality supplements. The dearth of knowledge related to potential adverse events after administration of these products is also concerning. At present, OJHSs are not required to be manufactured according to current Good Manufacturing Practices (cGMPs) like pharmaceutical drugs. Because there is no post-production monitoring of veterinary nutritional supplements, a myriad of poor quality supplements are available.5 This includes products that do not contain the amount of ingredient listed on the manufacturer’s label, products that recommend sub-therapeutic dosages, and nutritional supplements that are potentially contaminated by harmful components (such as heavy metals and/or pesticides) or by other
supplements manufactured in the same facility during the manufacturing process.

The purpose of this review is to critique the current body of evidence supporting the use of OJHSs in equine practice. This will include a description of cases in which OJHSs may be indicated, a recommendation for doses of OJHSs based on positive responses reported in published clinical trials, and an identification of when OJHSs could be considered contraindicated. OJHSs containing glucosamine, chondroitin sulfate, methylsulfonylmethane (MSM), and avocado/soybean unsaponifiable extracts (ASU) either alone or in combination formulations have been included, because these are the most commonly included and/or novel ingredients with the most research data available for discussion. In addition, the ACCLAIM system, (Table 1) a seven step guide to selecting supplements most likely to be beneficial, is described.

2. Indications and Dosing Recommendations

Osteoarthritis

In general, OJHSs are widely administered to horses with either a presumptive or definitive diagnosis of osteoarthritis (OA). To date, only two peer-reviewed studies have been performed in horses that support the use of OJHSs for OA. First, Hanson et al.8 administered a glucosamine/chondroitin sulfate combination product to 25 horses diagnosed with degenerative joint disease based on physical examination, diagnostic anesthesia, and radiographs/fluoroscopy. After 6 wk of treatment with the OJHS, significant improvements in lameness grade, flexion test grade, and stride length were noted compared with baseline measurements. No control/placebo group was included in this study, the examiners were not blinded to the treatment, and the horses were volunteered to participate in the study by owners. Further, the outcome measures are primarily subjective in nature. In this study, horses >545 kg were administered 14.4 g of glucosamine hydrochloride and 4.8 g of purified chondroitin sulfate per day. Horses <545 kg received 10.8 g of glucosamine hydrochloride and 3.6 g of purified chondroitin sulfate.

In a related study performed by Forsyth et al.7 in 1996, 20 veteran horses with joint degeneration were divided into either the treatment (n = 15) or placebo (n = 5) group. Horses <500 kg received a loading dose of 20 g of product per day (containing 4 g purified chondroitin sulfate, 10 g glucosamine hydrochloride, and 1 g N-acetyl-D-glucosamine) from day 1 to 35. From day 36 to 60, horses received 10 g of product per day (containing 2 g purified chondroitin sulfate, 5 g of glucosamine hydrochloride, and 0.5 g of N-acetyl-D-glucosamine). Horses >500 kg received 30 g of product per day on days 1–35 (containing 6 g purified chondroitin sulfate, 15 g glucosamine hydrochloride, and 1.5 g N-acetyl-D-glucosamine) and then 15 g of product per day until day 60 (containing 3 g purified chondroitin sulfate, 7.5 g of glucosamine hydrochloride, and 0.75 g N-acetyl-D-glucosamine). Beyond day 61, all horses were administered 10 g of product every other day.

This study found that the glucosamine/chondroitin sulfate combination product provided symptomatic relief to veteran horses. Significant improvements in range of joint motion, duration of swing, and length of stride were noted compared with pre-treatment assessment. Although this study included a control group and researchers were blinded to treatment, outcome measures could still be construed as subjective despite the use of video-recording devices and a two-dimensional (2D) motion analysis system for gait analysis. Further, horses included in this study were not diagnosed with any particular joint injury or disease; horses were selected simply based on age.

Navicular Syndrome

In addition to the study in horses with osteoarthritis, Hanson et al.8 also evaluated a glucosamine/chondroitin sulfate combination product in 14 horses diagnosed with navicular syndrome in a randomized, blinded, placebo-controlled trial. Outcome measures were predominantly subjective and included standing posture, response to hoof testers, flexion tests, lameness while trotting and lunging, and soundness after a 5-min warm-up. After 8 wk of treatment, no difference in radiographic characteristics (as determined either subjectively or using the MacGregor scoring system) of the navicular bones was noted; however, a significant improvement in lameness was noted in the treatment group (n = 8) compared with the control group (n = 6). Doses employed in this study included 9 g of a high-purity form of glucosamine hydrochloride and 3 g of a purified low molecular-weight sodium chondroitin sulfite administered orally twice daily.

Post-Traumatic/Post-Surgical

Rodgers9 studied the effect of a commercially available OJHS on the frequency of intra-articular injections in 10 competitive hunter/jumpers. This study was conducted over a period of 10 yr. It included a 2-yr baseline period before supplementation and an 8-yr period in which horses were supplemented with a glucosamine/chondroitin sulfate product. Included horses were evaluated for lameness throughout the study, and the number of times each horse was treated through intra-articular hyaluronan and corticosteroid was noted. Each 5.1-g scoop of the supplement contained 1200 mg glucosamine sodium sulfate, 1200 mg glucosamine potassium sulfate, 1200 mg glucosamine hydrochloride, 300 mg N-acetyl-D-glucosamine, and 1200 mg chondroitin sulfate. Horses reportedly received one 5.1-g scoop orally twice daily. The mean number of injections of the distal intertarsal and tarsometatarsal joints during the first 2 yr of the study was 1.7/yr, and the mean injection interval was 6.8 mo. During the 8 yr of supplementation, the mean number of injec-
tions decreased from 0.85 to 0.7/yr, and the mean injection interval increased from 9.98 to 10.82 mo. Based on these results, Rodgers\textsuperscript{9} concluded that daily supplementation with a commercially available OJHS resulted in a decreased requirement for intra-articular injections to maintain soundness in a group of competitive hunter/jumpers. This study was neither controlled nor blinded and relied on the subjective evaluation of lameness (diagnosis of distal tarsal pain/tarsitis by flexion, palpation, radiographic evaluation, and intra-articular anesthesia) by a single veterinarian and trainer. This study also did not comment on the trainer’s compliance in administering the supplement over the 8 yr of the study. As a result, the clinical relevance of these results is questionable from an evidence-based medicine approach.

In a recent study performed by Kawcak et al.,\textsuperscript{10} 16 horses were randomly divided into two groups, and an osteochondral defect was surgically created in one middle carpal joint of each horse. Horses in the treatment group were administered ASU extracts in molasses (total daily dose of ASU could not be determined based on the information included in the publication), whereas the placebo group received molasses only. Horses were trained on a treadmill from day 14 to 70, and various physical, biochemical, gross morphological, and histological features were assessed. Although no differences in signs of pain or lameness were identified, horses treated with ASU experienced a significant reduction in total gross examination scores (i.e., degree of articular cartilage erosion and synovial membrane hemorrhage) and a significant increase in articular cartilage glycosaminoglycan synthesis compared with the placebo group. Together, these results indicate that ASU possesses disease-modifying properties, which means that ASU supplementation results in positive structural effects in horses with OA.

In the United States, ASU is only available from one manufacturer, which was not the ASU product evaluated in the above described study by Kawcak et al.\textsuperscript{10} At present, ASU is commercially available in combination with glucosamine and chondroitin sulfate. The recommended maintenance dose for this product is 1 scoop daily for a \textasciitilde 600–1200-lb horse, and this dose contains 7.2 g glucosamine hydrochloride, 5 g MSM, 1.05 g avocado/soybean unsaponifiables powder, and 1.2 g sodium chondroitin sulfate. Although no in vivo studies evaluating the efficacy of this product have been published to date, several in vitro studies on its ASU ingredient and ASU, glucosamine, and chondroitin sulfate combination are currently available.\textsuperscript{11–16}

Prophylactic Use

In certain sectors of the equine industry, such as horse racing, OJHSs are used prophylactically before injury or trauma. The evidence for this usage is based on a canine study performed by Canapp et al.\textsuperscript{17} that supports the prophylactic administration of a glucosamine/chondroitin sulfate combination product. This study evaluated a glucosamine hydrochloride/chondroitin sulfate combination product (with or without S-adenosyl-L-methionine) in 32 dogs with an experimentally induced unilateral acute synovitis achieved by injecting the selected carpal joint with chymopapain. The randomized, double-blinded, placebo-controlled trial revealed that dogs treated with the supplement for 21 days before induction of the acute synovitis (n = 8) had significantly less evidence of joint inflammation compared with the control group (n = 8) and the dogs treated after the induction of the synovitis (n = 8). The prophylactically treated group of dogs had significantly lower lameness scores on days 12–19 as well as days 23 and 24 compared with the other groups. Inflammation was periodically assessed throughout the study period in all dogs using two-phase nuclear scintigraphy (i.e., soft tissue and bone phases), and lameness was subjectively evaluated by blinded investigators using a visual analog scale. Doses of the supplement used in this study exceeded the manufacturer’s recommendations. In short, the prophylactic use of OJHSs remains theoretical, but this is certainly an area worthy of further research.

3. Contraindications

In general, OJHSs are widely considered safe, and the reported LD\textsubscript{50} values (most often established in rats or mice) support this contention. In addition, one study evaluating the safety of a commercially available equine product containing a high purity, low molecular weight chondroitin sulfate and glucosamine hydrochloride has been performed.\textsuperscript{18} Six horses were administered 18 g of glucosamine hydrochloride and 6 g of chondroitin sulfate per day for 35 days; this is approximately five times the recommended daily maintenance dose. Results revealed minor alterations in hematological (hematocrit, hemoglobin, and white blood cell counts) and serum biochemical parameters (serum urea nitrogen, creatinine, calcium, phosphorus, potassium, total and indirect bilirubin, alkaline phosphatase, gamma-glutamyltransferase, lactic dehydrogenase, creatine kinase, and sodium-to-potassium ratio). None of these alterations were considered clinically significant and no other abnormalities were noted, including the results of the synovial fluid analysis. Therefore, this study concluded that this OJHS was safe in horses at the recommended dose. In a separate study, the commercially available ASU combination product was administered to 20 horses for 84 days. No significant differences in hematologic or serum biochemistry parameters or physical examination findings and no adverse events were reported in any of the included horses. Doses used in this study were \textasciitilde 36 g of glucosamine hydrochloride, 6 g of chondroitin sulfate, 5.25 g of ASU, and 25 g of MSM.\textsuperscript{19}
nutritional supplements are not an issue or that the lack of reported reactions is caused by the absence of a government-regulated reporting system (for veterinary supplements) akin to the system employed for pharmaceuticals. In humans, the FDA now requires that serious adverse events associated with nutritional supplement usage be reported.

Drug Interactions

During the preparation of this manuscript, no reports addressing drug interactions involving typical OJHS ingredients in either the human or veterinary literature were identified; however, drug-herb interactions have been reported. For example, yucca (Yucca schidigera) may accelerate NSAID metabolism, ginseng (Panax ginseng, Panax quinquefolius, or eleutherococcus senticosus) may interfere with drugs that are metabolized by the liver and may potentiate diuretics, flaxseed (Linum usitatissimum) may alter absorption of other drugs, and echinacea (E. purpurea, E. angustifolia, or E. pallida) may interact with drugs metabolized by the liver.

The safest way to address the issue of potential drug interactions is to maintain clear lines of communication with each client regarding their use of OJHSs and drugs or other nutritional supplements in their horse, which is also recommended in the human literature. In addition, any overt or suspected adverse event or drug reaction should be reported to the product manufacturer. At present, such reporting is voluntary; government guidelines do not mandate that adverse events be reported, and no reporting system is currently in place for veterinary nutritional supplements.

Insulin Resistance/Equine Metabolic Syndrome

In the human literature, the question of whether or not orally administered glucosamine negatively affects patients with type 2 diabetes mellitus or worsens insulin resistance has been explored after the observation that large IV doses of glucosamine induced insulin resistance in rats. The results from human studies have identified conflicting results. Pham et al. reported that oral glucosamine (at doses used to treat OA) worsened insulin resistance in individuals with poorer insulin sensitivity. In contrast, Muniyappa et al. reported that standard doses of oral glucosamine do not worsen insulin resistance in either lean or obese subjects. Finally, a placebo-controlled, double-blinded, randomized clinical trial performed by Scroggie et al. reported that the oral administration of 1.5 g of glucosamine hydrochloride and 1.2 g of chondroitin sulfate did not induce significant changes in glucose metabolism in patients with controlled type 2 diabetes mellitus as determined by hemoglobin A1C concentrations.

The impact of oral glucosamine administration on glucose metabolism has not been directly explored in horses; however, there is a theoretical risk that orally administered glucosamine, which is known to
be bioavailable, could induce or worsen insulin resistance/equine metabolic syndrome. Kirker-Head and Kirker-Head and Kettenacker and Griffin found no alterations in glucose levels in horses after the administration of high doses of glucosamine hydrochloride-containing OJHSs. Together, these results suggest that oral glucosamine does not alter glucose metabolism and does not seem to contribute to insulin resistance in horses. Considering the popularity of OJHSs in the older, less active equine population that might be at risk for insulin resistance, further research in this area may be warranted.

4. Seven Steps to Supplement Selection: The ACCLAIM System

As described by various research groups, poor quality supplements are widely available to unsuspecting consumers, including veterinarians. The preponderance of poor quality supplements makes recommending one or more products a clinical challenge. Using the seven-step ACCLAIM system devised by one of the authors (SO), practitioners can rapidly evaluate an OJHS based on information provided on the label to identify and recommend appropriate products.

1. Is the product in question manufactured by a company you recognize? In general, products manufactured by companies that have been in the industry for years that provide educational materials for veterinarians and consumers are preferable to the scores of OJHSs manufactured by newly formed companies. Established companies dedicated to improving the quality and efficacy of joint-health supplements are more likely to produce superior products.

2. Companies who support clinical research and have their products tested in clinical trials (e.g., for safety, efficacy, and bioavailability) that are published in peer-reviewed journals are more likely to have a quality product. These publications should be readily accessible to veterinary practitioners and companies should be able to send copies of their published research for your review. Some manufacturers claim to have their product tested but are subsequently unable to provide data or a reprint for evaluation. Three products evaluated in the study by Oke et al. claimed to have published research trials. One company had multiple publications, whereas the remaining two companies each claimed to have a single publication supporting their product. Both of these latter two companies manufactured products that did not contain the amount of glucosamine that was listed on the product label.

3. In terms of the product contents, all ingredients, including the active ingredients, inactive ingredients, and fillers, should be clearly indicated on the product label. Products that do not contain the amount of ingredients as listed on the product label likely contain other fillers or ingredients that are not identified, and they may, therefore, pose a potential health risk to the horse or the person administering the supplement.

4. Other features to note on the manufacturer-generated label are product claims. If the claims sound too good to be true, they probably are. Products with realistic label claims based on scientific study results, rather than testimonials, are preferable. Although the FDA has regulations regarding the type of claims that can be made on a nutritional supplement (i.e., label claims must be truthful and not misleading), illegal claims such as those claiming to diagnose, treat, cure, or prevent a disease are abundant. Products with illegal claims should be avoided.

5. Dosing instructions should be accurate and easy to follow. The amount of active ingredient administered per dose per day should be easily calculated. Companies that use several different units on their product make dose calculations challenging and time consuming. For example, a product may have some ingredients listed in milligrams and others in ounces, but the overall dosing instructions are based on scoops. Furthermore, the amount of ingredients per scoop is not detailed, which makes the label deliberately confusing to the consumer or veterinarian. Products with clear administration recommendations and recommended dosages based on published clinical trials are more likely to be effective.

6. Products with a lot identification number or some other tracking system suggest that some form of pre- and/or post-market surveillance system to ensure product quality is in place. In addition, companies that have voluntarily instituted cGMPs and other quality control/quality assurance techniques (e.g., tamper-resistant packaging and individual tablet/caplet identification) are more likely to be reputable, because each of these procedures is costly. Producing a supplement akin to a pharmaceutical drug shows a long-term investment into their product and company.

7. Manufacturer information should be clearly stated on the label, preferably in concert with contact information or a website for customer support. Companies may also employ veterinarians on staff to answer technical questions or issues.
5. Where Is the Evidence?

As indicated throughout this review, the available evidence supporting or refuting the use of OJHSs in equine practice is limited. In vivo studies are challenging in veterinary medicine, particularly in horses, largely because of a combination of ethical, economic, and logistical issues. One major hurdle in the nutritional supplement industry is that the supplements are already extremely popular, which ultimately deters manufacturers from “wasting” their profits on research studies for products consumers are already using. Furthermore, companies that do perform legitimate research studies often suffer from the “coat-tail phenomenon” in which companies that do not perform their own research claim that their product will have similar results as the tested products.

Practitioners are encouraged to take an evidence-based medical approach to assess existing and future in vivo studies. This will enable veterinarians to recommend quality products based on the best available evidence. As described by Wright39 in a 2007 communication published in the Journal of Bone and Joint Surgery, a level-of-evidence rating can be assigned to all clinical trials to concisely and easily evaluate the study’s overall quality and therefore, critically assess the study’s take home message. Wright39 describes studies from level I (randomized and controlled studies) to level IV (case series) and summarizes that, in general, controlled clinical trials, prospective studies, and randomized studies are superior to non-controlled, retrospective, and non-randomized trials. Progress in this field of veterinary medicine will only occur when consumers, including veterinarians, demand additional research and adopt evidence-based medicine.

6. Conclusion

Published clinical trials support the use of glucosamine, chondroitin sulfate, and/or ASU in horses with OA and navicular syndrome. These drugs are also effective post-surgically and post-traumatically. Evidence in dogs suggests that OJHSs may also be beneficial when administered prophylactically. Nonetheless, there is an obvious need for additional, non-subjective, randomized, controlled clinical trials evaluating the efficacy of equine OJHSs with adequate power to confirm or refute the clinical indications of these supplements. Despite the high LD50 values associated with many ingredients included in OJHSs, potential contraindications associated with the use of OJHSs do exist and are worth considering when recommending nutritional supplements. Finally, selecting a quality nutritional supplement can be rapidly achieved using the ACCLAIM system. Veterinarians should take an evidence-based approach when evaluating nutritional supplements, including OJHSs, just as they do with pharmaceuticals. By following the recommendations in this review, practitioners can confidently recommend safe and effective OJHSs to their clients.

Dr. Stacey Oke is a paid consultant of Nutramax Laboratories, Inc. and other pharmaceutical and nutritional supplement companies. Dr. Wayne Mellwraith has no relevant disclosures.

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