Kentucky Equine Research®
World Leaders In Equine Nutrition

Advances in Equine Nutrition

Volume II

Edited by

J.D. Pagan

NUTRACEUTICALS: WHAT ARE THEY AND DO THEY WORK?

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Introduction

In the past five years, the world has witnessed the explosive growth of a multi-billion dollar industry known as nutraceuticals. The term "nutraceutical" combines the word "nutrient" (a nourishing food or food component) with "pharmaceutical" (a medical drug). The word "nutraceutical" has been used to describe a broad list of products sold under the premise of being dietary supplements (i.e. a food), but for the expressed intent of treatment or prevention of disease. What is the legal definition of a nutraceutical? How do they differ from either a nutrient or a drug? What rules govern their safety and efficacy? What nutraceuticals have found their way into the horse industry? These topics will be addressed in the following paper.

By Definition

Several terms need to be defined in order to gain an understanding of nutraceuticals.

Nutrient: As defined by AAFCO (1996), "a feed constituent in a form and at a level that will help support the life of an animal." The chief classes of feed nutrients are proteins, fats, carbohydrates, minerals and vitamins.
Feed: As defined by AAFCO (1996), "edible materials which are consumed by animals and contribute energy and/or nutrients to the animal's diet."
Food: As defined by the Food, Drug and Cosmetic Act (1968), "an article that provides taste, aroma or nutritive value. Food and Drug Administration (FDA) considers food as 'generally recognized as safe' (GRAS)."
Drug: As defined by AAFCO (1996), "a substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals. A substance other than food intended to affect the structure or any function of the body of man or other animals."
Dietary Supplement: As defined by the Dietary Supplement Health and Education Act (DSHEA, 1994), "a product that contains one or more of the following dietary ingredients: vitamin, mineral, herb, or other botanical, and amino acid (protein). Includes any possible component of the diet as well as concentrates, constituents, extracts or metabolites of these compounds."
Nutraceutical: As commonly defined by the dietary supplement industry, "any nontoxic food component that has scientifically proven health benefits, including disease treatment and prevention."
Veterinary Nutraceutical: As defined by the newly created North American Veterinarian Nutraceutical Council, Inc. (NAVNC), "a substance which is

produced in a purified or extracted form and administered orally to patients to provide agents required for normal body structure and function and administered with the intent of improving the health and well-being of animals."

Food or Drug

Using the above definitions, it is still difficult to determine what is and what isn't a nutraceutical. Are nutraceuticals considered food or feeds? According to definition, a feed is an edible substance that contributes energy or nutrients to an animal's diet. Feeds can make claims only about the nutrients they contain and the scientific functions of those nutrients. Both of the definitions presented in this paper for nutraceuticals either include the word "food" or state they are "required for normal body structure and function." A potential difference between a feed and a nutraceutical is that a nutraceutical is unlikely to have an established nutritive value (Boothe, 1997). Feeds are required to have nutritive value and are accountable, via labeling, for these values. Another difference between a feed (food) and a nutraceutical is that feed is generally recognized as safe (GRAS). Nutraceuticals may contain substances that are "natural" but may not be generally recognized as safe.

The other component of our definition of nutraceutical includes the statements "for disease treatment and prevention" and "administered with the intent of improving the health and well-being of animals." When a dietary supplement, nutraceutical or other feed is intended to be used for the treatment or prevention of disease, in essence it "becomes" a drug (Dzanis, 1998). Drugs are subject to an approval process prior to marketing. To be approved, a drug must demonstrate safety and efficacy for its intended use (Dzanis, 1998). Drugs that are not properly approved are subject to regulatory action. Nutraceuticals are not drugs simply because they have not gone through an approval process (Boothe, 1997).

From this discussion, it seems nutraceuticals fall somewhere in between food and drug. They have many advantages over either food or drug since they are not required to list nutrient profiles as required by feeds, and in many cases are intended to treat or prevent disease without first undergoing proper drug approval. Determining if a product is a food, or is subject to regulation as a drug, is a function of the manufacturer's claims that establish intent. Boothe (1997) cites the example of vitamin E. When vitamin E is added to the diet as an essential nutrient it is considered a feed component. However, when vitamin E is claimed to treat or prevent azoturia (tying-up) in horses, it is a drug.

Regulations

The primary set of rules governing the human nutraceutical market is the Dietary Supplement Health and Education Act (DSHEA) passed in 1994. This act does not permit FDA to consider a new product a "drug" or "food additive" if it falls under the definition of a "dietary supplement," which includes among other substances any possible component of the diet as well as concentrates, constituents,

extracts or metabolites of these components (Dzanis, 1998). This gives human nutraceutical manufacturers a wide range of substances that may be able to satisfy these requirements. The other major component of this act shifts the burden of safety. The FDA now has to prove a substance is unsafe rather than the manufacturer proving the substance safe (Dzanis, 1998).

The DSHEA rules do not apply to nutraceuticals intended for animals. In a nutshell, the federal government has cited differences in metabolism of substances between humans and animals and potential safety issues with nutraceuticals used in food producing animals as reasons to exclude animals from provisions of the DSHEA. Therefore, expressed or implied claims relating use of a product with the treatment or prevention of disease, or with an effect on the structure or function of the body in a manner distinct from what would be normally ascribed to "food" (e.g. that it does something other than provide known essential nutrients), could cause a product to be subject to regulation as an unapproved "drug" (Dzanis, 1998).

Safety and Efficacy

Many nutraceuticals are being used as alternatives for both nutrition and medicine. A substantial number of these products make illegal drug claims without regulation and proper data to support their safety and efficacy. As such, consumers need assurance that a product is safe and hopefully able to do what it say it does.

Above anything else, nutraceuticals should be safe. Stock should not be taken in the old adages "if a little is good, a lot is better" or "it can't hurt." Nutraceuticals, like many substances, may cause problems due to direct toxic effects, or by delay of more appropriate treatment (Dzanis, 1998). Safety of a nutraceutical product is often easier to establish than efficacy. Studies that test doses of nutraceutical several fold greater than the intended (recommended) dose help to establish toxicity data. These studies must test animal reaction to the product both short- and long-term. Finally, a lack of reported toxicity problems with any nutraceutical should not be interpreted as evidence of safety (Boothe, 1998).

Does the nutraceutical do what it says it can do? Is the product effective? Evidence of efficacy is generally provided by studies that document the pharmaceutical, pharmacokinetic, and pharmacodynamic characteristics of a compound (Boothe, 1998). Pharmaceutical data are an evaluation of quality of manufacturing, purity of product and accuracy of labeling. Pharmacokinetic data consists of tracking the compound through the animal's body. It also answers questions about absorption, tissue distribution, metabolism and excretion. Pharmacodynamic evaluation describes how the animal responds to the compound. This step is the most difficult to define for nutraceuticals since most of these compounds are involved in a cascade of different reactions throughout the body.

Since the market for nutraceuticals is booming, many products are available that have not been tested for either safety or efficacy. A simple test of a quality nutraceutical product may be to ask for research data (peer reviewed and published)

which support the product. This will go a long way in limiting quackery and the ever present danger of parting you from your money.

Nutraceuticals and the Horse

The theory behind the mode of action of nutraceuticals is to provide functional benefits by increasing the supply of natural building blocks in the body. Replacement of these building blocks can work in two ways: to diminish disease signs or to improve performance. The use of nutraceuticals as performance enhancers is much more common than treatment of disease.

Much of the data used to promote nutraceuticals to the public come from human research. There are only a limited number of nutraceuticals in which research has been done in the horse. For this reason, we will discuss only products that have at least had preliminary testing in the horse. The following is a brief discussion of the theorized mode of action, a summary of human studies and results of equine research.

Carnitine

Carnitine is an amino acid found in abundance in cardiac and skeletal muscle. Since carnitine is involved with the utilization of fatty acids for energy in the muscle cell, it has been hypothesized that supplementation of carnitine would be glycogen sparing and reduce lactic acid production. The end result would be improved muscle function and endurance. While human studies have not been able to show an increase in muscle carnitine from supplementation or improvement in performance with healthy individuals, improvement in humans with impaired oxygen supply was seen in heart and skeletal muscle from carnitine supplementation (Cerretelli and Marconi, 1990). Endogenous synthesis, primarily in the liver, is probably adequate in the normal healthy adult but may be deficient at times of stress and in certain disease states.

The carnivorous human diet is typically very high in carnitine, while the herbivore diet is very low and the horse will have to produce the majority of its carnitine supply endogenously. Taking this into consideration, researchers have investigated responsiveness of yearlings and adult horses to oral carnitine supplementation in adult and yearlings. Results are somewhat inconclusive in that supplementation increased plasma free carnitine in adult and most yearling horses, while long term feeding did not increase muscle carnitine concentrations. Since an increase in muscle carnitine is what would improve performance, there is no evidence in the horse that supplementation really helps.

Coenzyme Q_{10}

Ubiquinone, more commonly known as coenzyme Q_{10}, is a substance found in the body as a component of the mitochondrial respiratory chain. It works in concert with other substances to regenerate ATP (energy) in a cell. Coenzyme Q_{10} also functions as a powerful antioxidant and free radical scavenger. An antioxidant is a substance that gives up electrons easily and can act to neutralize

harmful oxidants and free radicals. In humans, the levels of coenzyme Q_{10} have been found to be below normal in patients with cardiovascular disease and periodontal disease. Whether low levels are a cause or effect is not clear, but coenzyme Q_{10} supplementation has been reported to have been used successfully in the treatment of heart problems, muscular dystrophy, myopathies and periodontal disease (Greenburg and Fishman, 1990; Nishikawa et al., 1989). Use of coenzyme Q_{10} is not very well researched in the horse. One study found that coenzyme Q_{10} may have an indirect effect on the utilization of oxygen within the tissues, but had no effect on lactate metabolism or heart rates (Rathgeber-Lawrence et al., 1991). Perhaps the use of coenzyme Q_{10} in the horse has potential in treatment of heart and muscle disorders, but it needs to be investigated further.

Creatine

The idea behind creatine supplementation is that increasing the creatine content of muscle will increase the corresponding creatine phosphate (PCr) concentration. A simple reaction involving creatine phosphate is the muscle cell's first and fastest source of energy for contraction. It is present in limited amounts in the muscle cell and has a fairly rapid turnover rate. The availability of PCr has been proposed as one of the most likely limitations to muscle performance during intense, fatiguing, short-term exercise. Scientific investigations in humans indicated that the PCr content of muscle was increased by taking creatine supplements, and that exercise performance is improved by ingestion of creatine over a period of days prior to the exercise test (Greenhaff et al., 1993; Harris et al., 1993). However, in another study 30% of subjects ingesting creatine failed to show an increase in muscle creatine or retain substantial quantities (Greenhaff et al., 1994). One major problem with creatine supplementation is the frequency that the supplement has to be taken (4-6 x per day) which makes it impractical for the horse. One study done in racing Thoroughbred horses failed to show marked increases in muscle creatine after supplementation and no improvement in performance (Sewell and Harris, 1995).

DMG

Dimethylglycine (DMG), a derivative of the amino acid glycine, is a normal intermediate in choline metabolism and has been proposed to enhance creatine phosphate stores in muscles. Many of the claims of the benefits of DMG supplementation are to increase oxygen utilization, reduce lactic acid accumulation in the muscles, strengthen the horse's natural immune response system, prevent tying-up, increase a horse's tolerance to vigorous physical activity and improve overall performance. DMG first came to the forefront when it was found that the Russian athletes were using the "super drug" that they called vitamin B15 or pangamic acid as a performance enhancer. There has been work done in humans receiving DMG orally which suggests that it will boost the immune system (Sellnow, 1987). The use of DMG in the horse has been studied more than most nutraceuticals, but still far from extensively, with mixed results. Studies on supplementation of DMG to Standardbreds and Quarter horses found reduced

blood lactate, while a third study with Thoroughbreds found no benefit (Levine et at., 1982; Moffit et al., 1985; Rose et al., 1989). The fervor over DMG has died down and little work has been done on the subject in recent years.

HMB

ß-hydroxy-ß-methylbutyrate or more simply HMB is a product made in the muscle tissue from the amino acid leucine. Once HMB is formed it serves as a building block for intramuscular cholesterol synthesis. During stressful situations like heavy training and exercise, it is theorized that the muscle cell may not be able to make enough cholesterol for maximal growth or function. Supplying HMB in the diet supposedly would keep blood cholesterol at an optimal level. Work in humans has indicated that aerobic exercise performance and muscular strength can both be improved with HMB supplementation. Very recent studies in Thoroughbreds show promise for the nutraceutical. A treadmill study found lower muscle tissue breakdown in HMB supplemented horses with higher blood glucose during exercise than controls (Nissen et al., 1997). One study with horses in actual race training and racing conditions found a lower amount of muscle enzymes (indicative of muscle damage) in the HMB supplemented horses after a race (Miller and Fuller, 1998). The general impression of HMB supplementation was that it allowed the horses to condition faster.

MSM

Methylsulfonylmethane (MSM) is an odorless and tasteless derivative of the pungent dimethylsulfoxide (DMSO). Its main action is to supply bioavailable sulfur to the horse, and it has been proclaimed to have numerous beneficial effects: moderating allergic reactions and gastrointestinal tract upset, correcting malabsorption of other nutrients (in particular minerals related to developmental orthopedic disease), relieving pain and inflammation, acting as a natural antimicrobial, antioxidant and antiparasitic. Exactly where MSM goes in the body after ingestion has been studied intensively (Metcalf, 1983). With the help of tracer studies, it appears that MSM given orally will eventually end up in every cell in organosulfur molecules. Effectiveness of MSM in treating all of the above stated conditions to this date is mostly anecdotal.

Oral Joint Supplements

The intent of oral joint supplements is to 1) work as an anti-inflammatory agent and/or 2) supply additional building blocks for the formation and maintenance of normal joint cartilage. Ultimately, the idea is to make movement in the joint less painful for the individual. Most oral joint supplements contain chondroitin sulfate and/or glucosamine. Joint supplementation is one area of research where the work done in the horse stimulated interest for use of the products in the human. The most intriguing question about oral joint supplements is whether the product gets to the joint in order to help. The fact that oral supplementation does at least get the product into the bloodstream has been established (Baici et al., 1992). There is a study currently underway looking at the arrival of the products from the

bloodstream to the joint being done by researchers at Marion DuPont Equine Medical Center. Experimental evidence of effectiveness of oral joint supplements on improvement of lameness in horses would indicate that at least some of the product is getting to the joint (Hanson et al., 1996). Certainly, this type of nutraceutical is one area where a flourish of research can be expected in the coming years.

Conclusion

It becomes blatantly clear from the brief summaries above that product testing in the horse is sparse for the number of nutraceuticals available on the market. Since efficacy and safety testing are not required in order to market a product (as long as the product does not have medicinal or performance enhancing claims on the label or in the literature), it is difficult to say whether the testing will ever be done. Certainly, if testing ever became required for nutraceuticals, the resulting increase in price of the products may make them prohibitively expensive. Because of the lack of regulation for these products, horse owners themselves become the researchers and their beloved horses the subjects in their own fact finding missions on the truth and efficacy of the nutraceutical.

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