Mode of Action of Oral Chondroprotective Agents in Equine Practice

Cartilage replenishes its major components by manufacturing and remodeling prodigious amounts of collagen and proteoglycans. This constant and ongoing synthesizing process often generates extremely large demands for building blocks of collagen and proteoglycans. If the raw materials (nutrients) for these building blocks are not available in the amounts required, the synthesizing process is impaired and the cartilage loses its ability to replenish itself.

Chondroprotective agents are defined as compounds that support or enhance macromolecular synthesis by chondrocytes; support or enhance synthesis of hyaluronic acid by synoviocytes in synovial fluid; inhibit degredative enzymes (collagenase, hyaluronidase), or inflammatory mediators (interleukin-1, tumor necrosis factor); and remove or prevent formation of fibrin, thrombin, and plaque in synovium and/or subchondral blood vessels. Compounds which are capable of these actions are the same ones the body uses to manufacture proteoglycans (PG), especially glycosaminoglycans (GAGs).

Chondrocytes obtain glucosamine preformed from the circulation, or synthesize it from glucose and amino acids. Once glucosamine is formed, it is used for GAG synthesis. Regardless of the source, glucosamine levels are critical to subsequent macromolecular synthesis. This is why exogenous sources of glucosamine can be beneficial for GAG synthesis.

Glucosamine is then used directly for synthesis of hyaluronic acid, and for all other GAGs after conversion to amino sugars by epimerases. Thus, glucosamine is more than just the major building block of GAGs, glucosamine is also a key up-regulator of GAG synthesis (and thus cartilage matrix synthesis). Glucosamine has been shown to stimulate GAG, PG, and collagen synthesis in chondrocytes and fibroblasts. Its mechanism of action is quite simple: providing the regulatory stimulus and raw materials for the synthesis of GAGs.

Glucosamine salts are easily absorbed and are distributed to cartilage, where they have been shown to be incorporated into the cartilage matrix. These salts have passed all the tests required for safety, bioavailability, uptake into target tissue, and effective actions at tissue concentrations reached by oral administration. Glucosamine salts have been shown to be chondroprotective by enhancing macromolecular synthesis of chondrocytes and supporting the synthesis of hyaluronic acid by synoviocytes in synovial fluid.

Chondroitin sulfates (CS) are long-chain polymers of a repeating disaccharide unit: galactosamine sulfate and glucuronic acid. Quantitatively they are the major GAGs found in cartilage. When oral administrations of CS are given to patients with osteoarthritis, similar results to glucosamine salts were found: reduction in pain and improvement in joint function. In vitro, CS was an effective and direct inhibitor of degredative enzyme activity. In long-term clinical trials of injectable CS, the course of osteoarthritis was greatly slowed, joint function improved, joint pain and analgesic usage reduced, radiographic evidence of reversal was seen, and previously disabled subjects were able to return to work.

Chondroitin sulfates are readily bioavailable as intact chains, monomer subunits and the spectrum of chain lengths in between. Inhibition of enzymes that degrade cartilage is accomplished at low concentrations, which are attainable after either injectable or sustained oral administration. CS has the ability to stimulate GAG and collagen synthesis in chondrocytes. Chondroitin sulfates have shown evidence of being chondroprotective by enhancing synthesis of chondrocytes, inhibiting degredative enzymes and inflammatory mediators, and preventing the formation of fibrin and/or thrombin in the synovium and/or subchondral blood vessels.

Both glucosamine salts and chondroitin sulfates have proven bioavailability and clinical benefits. Glucosamine salts stimulate GAG synthesis while chondroitin sulfates inhibit degredative enzymes, thereby improving nutrient supply to the cartilage. Therefore, a combination of glucosamine salts and chondroitin sulfates provides each part of the definition of a chondroprotective agent. The combination of these two produces a synergistic effect because low molecular weight glucosamine salts and high molecular weight chondroitin sulfates have overlapping and unique functions to prevent damage to connective tissue.

Chondroprotective agents can be used in a maintenance program as protection against articular cartilage degeneration. They can also be used where articular cartilage deterioration has already occurred due to injury or stress-related joint damage. The response time is dose-related and dependent upon the severity of the condition.

With new products like Cosequin® (Nutramax Laboratories, Inc., Baltimore, MD) which is a patented combination of glucosamine and purified chondroitin sulfates, the nutritional approach for the treatment of osteoarthritis looks very promising. The logical future of chondroprotection will involve determining and correcting abnormal joint load forces, providing chondroprotective nutritional agents, improving health and exercise habits in general, and judicious use of selected analgesics as needed.

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