Zoledronic Acid for Canine Osteoarthritis

The bisphosphonate group is a drug class evaluated and used for its modulatory effects on bone. Bisphosphonates reduce bone resorption by acting on recruitment, activity, or life span of osteoclasts. This study investigated the effects of zoledronic acid on preservation of subchondral bone in an experimental model of cranial cruciate ligament (CrCL) disease.

The left CrCL was surgically transected in adult dogs (n = 21). Dogs were stratified into 3 equal groups: control, low-dose zoledronic acid (10 µg/kg), and high-dose zoledronic acid (25 µg/kg). Injections were given q3mo SC for 1 year. Biochemical markers of collagen synthesis and destruction, bone-specific ALP, and indicators of cartilage turnover were measured at intervals over 12 months. Animals were euthanized, and necropsies were performed after 1 year.

Zoledronic acid was found to provide chondroprotective effects on articular cartilage, quantified as a combination of macroscopic and biochemical changes on samples obtained 1 year after CrCL transection. The protective effect was identified primarily as a reduced number of cartilage lesions in the high-dose group. Effects may have been partially mediated by regulation of collagenase activity, as types I and II collagen concentrations were significantly reduced in synovial fluid from bisphosphonate-treated dogs. Osteophyte count was not affected by zoledronic acid; therefore, radiographic osteoarthritis (OA) scores did not reflect chondroprotective drug benefits.

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### Source


### Commentary

Zoledronic acid (zoledronate) is a newer-generation bisphosphonate that is expensive, but safe and relatively easy to use. The drug is under investigation as a palliative measure in dogs with appendicular osteosarcoma that are not candidates for limb amputation and is also anecdotally given as an adjunctive measure to patients undergoing CyberKnife radiation as a limb-sparing procedure. Based on study results, zoledronic acid may also be useful in OA cases. Because the chondroprotective effects supposedly took months to occur and the experimental model was an acute insult (no prior history of OA), it is unclear which animals with OA would benefit from the treatment (eg, the dog with CrCL rupture undergoing surgery or the 12-year-old Labrador retriever with multifocal OA and joint derangement). It is also unclear whether the drug provided pain relief or improved joint function. Zoledronate has been shown to cause osteomalacia of the jaw with chronic use in humans, with further studies regarding long-term use are warranted in animals.—Heather Troyer, DVM, DABVP, CVA

### Post-Approval Experience: (Rev 2010)

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration
Urinary: azotemia, elevated creatinine, renal failure
Neuromuscular: behavior alteration, depression
Hepatic: elevated liver enzymes
Dermatologic: pruritus

Death has been reported as an outcome of the adverse events listed above. Acute renal failure and death have been associated with use of meloxicam in cats.

**Effectiveness:** The effectiveness of meloxicam was demonstrated in two field studies involving a total of 227 dogs with CrCL disease, both involving various breeds and age groups. Dogs were studied 6 months and 12 months of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked, clinical studies showed that dogs received 0.2 mg/kg on day 1. All dogs were maintained on 0.1 mg/kg meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n = 11), dogs showed clinical improvement with statistical significance after 4 days of meloxicam treatment for all parameters. In the second field study (n = 46), dogs receiving meloxicam showed a clinical improvement. At 14 days, clinical improvement for all parameters was noted by the overall investigator evaluating on day 7, and for the owner evaluation on day 7.

**How Supplied:** Meloxicam 1.5 mg/ml, Oral Suspension: 10, 32, 100 and 200 ml, individual or multi-dose oral suspension bottles with small and large dosing syringes.

**Storage:** Store at controlled room temperature 68-77° F (20-25° C).

**Warning:** Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. For veterinary use only.

**Cautions:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**Indications:** Meloxicam Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

**Contraindications:** Dogs with known hypersensitivity to meloxicam should not receive Meloxicam Oral Suspension. Do not use Meloxicam Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.

**Warnings:** Not for use in animals all of which of children. Consult a physician in case of accidental ingestion by humans. For veterinary use only.

**Precautions:** The use of Meloxicam in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. Meloxicam Oral Suspension is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. As a class, cyclooxygenase-inhibiting NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concurrent diuretic therapy, or those with existing renal, cardiac, or hepatic disease. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the production of prostaglandins that maintain renal homeostasis. Such antiprostaglandin effects may result in clinically significant renal disease in patients who have not been previously diagnosed. Since NSAIDs possess the potential to reduce gastrointestinal ulcerations and/ or perforations, concurrent use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. Additional pain medication is needed after administration of the total daily dose of Meloxicam Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be continued. The use of another NSAID is not recommended. Consider appropriate washout times when switching from cyclooxygenase inhibition to cats from one NSAID to another in dogs. The use of concurrent potent-protein binds drugs with Meloxicam Oral Suspension has not been studied in dogs. Commonly used protein-bound drugs include indocid, antiarrhythmic and behavioral medications. The influence of concurrent drugs that may inhibit metabolism of Meloxicam Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

**Adverse Reactions:** Fatal toxicity was evaluated in 506 dogs. Based on the results of two studies, GL abnormalities (vomiting, soft stools, diarrhea, and increased water consumption) were the most common reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the studies. Dogs may have experienced more than one episode of the adverse reaction during the study. In foreign suspected adverse drug reaction (SADR) reporting over a 9 year period, incidences of adverse events associated with meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyurethia (3 dogs), nephropathy (1 dog), and nephritis (1 dog).