

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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■ 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^{1,2} and is 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 cancer, so further studies regarding long-term use are warranted in animals.—*Heather Troyer, DVM, DABVP, CVA*

■ ■ Source

Chondroprotective effects of zoledronic acid on articular cartilage in dogs with experimentally induced osteoarthritis. Dearmin MG, Trumble TN, García AP, et al. *AM J VET RES* 75:329-337, 2014.

1. **Zoledronic acid for the treatment of appendicular osteosarcoma in a dog.** Spugnini EP, Vincenzi B, Caruso G, et al. *J Small Anim Pract* 50:44-46, 2009.
2. **Effect of zoledronic acid and amputation on bone invasion and lung metastasis of canine osteosarcoma in nude mice.** Wolfe TD, Pillai SP, Hildreth BE 3rd, et al. *Clin Exp Metastasis* 28:377-389, 2011.

Meloxidyl® (meloxicam)

ANADA 200-550, approved by the FDA.
*Please read entire package insert before use.

Meloxidyl®
(meloxicam) 1.5 mg/mL Oral Suspension

Non-steroidal anti-inflammatory drug for oral use in dogs only

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

Indications: Meloxidyl 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 Meloxidyl Oral Suspension. **Do not use Meloxidyl Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.**

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Warnings: 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 oral use in dogs only.**

As with any NSAID all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration. Owner should be advised to observe their dog for signs of potential drug toxicity and be given a client information sheet about Meloxidyl Oral Suspension.

Precautions: The safe use of Meloxidyl Oral Suspension 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, cyclo-oxygenase inhibitory 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 concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concomitant administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such antiprostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after administration of the total daily dose of Meloxidyl Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Meloxidyl Oral Suspension has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Meloxidyl Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Adverse Reactions: Field safety was evaluated in 306 dogs. Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetence) were the most common adverse 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 reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Clinical Observation	Meloxicam (n=157)	Placebo (n=149)
Vomiting	49	23
Diarrhea/Soft Stool	19	11
Bloody Stool	1	0
Inappetence	5	0
Bleeding Gums After Dental Procedure	1	0
Lethargy/Weakness/Depression	1	0
Eyes	1	0

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/CVMA. 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
Neurological/Behavioral: lethargy; 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 representing various breeds, between six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study ($n = 109$), dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all parameters. In the second field study ($n = 48$), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.

How Supplied: Meloxidyl® 1.5 mg/mL Oral Suspension: 10, 32, 100 and 200 mL bottles with small and large dosing syringes.

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

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