

Current and future trends in the use of NSAIDs for the treatment of osteoarthritis in dogs

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inflammatory mediators and their interactions in the inflammatory cascade, as well as new data on the biochemical mediators associated with osteoarthritis, have led to increased use of NSAIDs. The arrival of NSAIDs with better defined safety and efficacy profiles for dogs has also dramatically increased their use. NSAIDs are known to provide analgesia, antiinflammatory and antipyretic capabilities, yet the exact mechanisms of action for this group of drugs is still being elucidated.

The classic explanation of their antiinflammatory mode of action is inhibition of the cyclooxygenase (COX) enzymes. These enzymes are active in the metabolism of arachidonic acid. Furthermore, certain NSAIDs may have selectivity in their actions against these isoenzymes of cyclooxygenase. Likewise, conventional thinking states that NSAIDs act peripherally to provide analgesia. However, recent data also support a central mechanism of action for pain modulation, which may account for a significant portion of the therapeutic benefits they provide when treating osteoarthritis (OA). With these new insights, this article focuses on products used in the management of osteoarthritis.

KEY POINTS

- Most nonsteroidal antiinflammatory agents (NSAIDs) exert their effect by inhibiting cyclooxygenase.
- NSAIDs do not halt or reverse the underlying disease process but they palliate pain and restore clinical function to patients.
- The clinical response to a particular drug is quite individualistic.
- The most common problems associated with NSAID administration in dogs involve the GI tract.
- Every effort should be made to prevent, rather than treat, the adverse reactions associated with NSAID use.
- NSAIDs should not be used alone in the management of osteoarthritis. Every effort must also be put into strategies to modify body weight, including exercise and physiotherapy.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) have been available to small animal practitioners for many years, but their use has remained relatively uncommon. Recently, new discoveries about

PHARMACOKINETICS AND MECHANISMS OF ACTION

NSAIDs derive much of their antiinflammatory properties from their capacity to inhibit the synthesis of prostaglandins (**Figure 1**). Prostaglandins are released in response to injury and have the capacity to provoke vasodilatation, erythema, and hyperalgesia (1). Vane, in 1971, demonstrated that aspirin decreases prostaglandin synthesis through the inhibition of cyclooxygenase (2). More

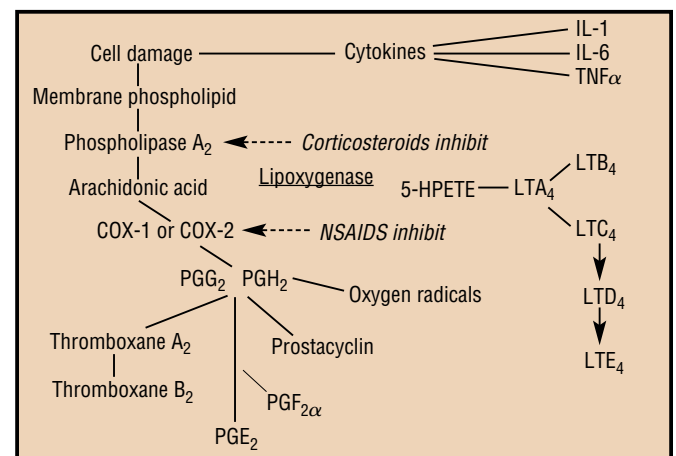


Figure 1 Pathways of pro-inflammatory mediators after cell membrane damage.

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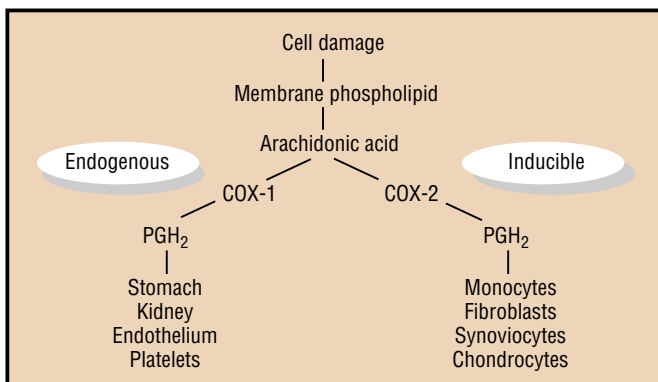


Figure 2 Pathways and target tissues of COX-1 (Endogenous) and COX-2 (Inducible) enzymes in arachidonic acid metabolism.

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recently, discoveries have documented two forms of cyclooxygenase (3, 4). These have been identified as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is considered to be the constitutive form, as it is important for normal physiological functions. COX-2 is considered to be an inducible form of the enzyme, and is associated with inflammation and pain (Figure 2).

Theoretically, an NSAID that selectively inhibits COX-2 without affecting COX-1 will allow analgesia without the common side effects of COX-1 inhibition, which include altered gastrointestinal (GI), renal and thrombocyte function. This hypothesis has not yet been proven clinically in patients (5). When examining a particular product, the ability to inhibit each enzyme is reported as a ratio and is used to define enzyme selectivity. These ratios must be examined carefully as different reports may have COX-1 as the denominator or numerator. There is currently little data to support direct correlation of any of these different *in vitro* testing techniques with clinical efficacy and safety. In addition, extensive data exists that many of the antiinflammatory effects of NSAIDs are unrelated to the inhibition of arachidonic acid metabolism. NSAIDs have been shown to inhibit a variety of functions of neutrophils, including adhesiveness, aggregation, chemotaxis, degranulation, and superoxide anion generations (1, 5).

One additional aspect of chronic NSAID administration for the treatment of OA is the potential effects the drug may have on the chondrocyte metabolism. Depending on the specific product, there is primarily *in vitro* data that supports the claim of both articular cartilage sparing effects and potentiation of damage to the articular cartilage. It must be reiterated that effects of pharmaceuticals on cartilage metabolism *in vitro* are not necessarily of significance *in vivo*. It must also be noted that the degree of damage to the cartilage in question may have a very important role in rendering it vulnerable to the metabolic effects of these drugs. Thus information on *in vitro* cartilage effects presented here should not be the sole factor in the decision on which product to use in an individual case.

USE OF NSAIDS IN THE MANAGEMENT OF OA

The abilities of NSAIDs to relieve clinical signs of OA (Figures 3–7) is common knowledge in small animal practice. Despite the fact that NSAIDs do not halt or reverse the underlying disease process, they are frequently used since they palliate pain and restore normal function to our patients (Table 1). The number of approved NSAIDs available to the veterinarian around the world includes, but is not limited to, carprofen, etodolac, ketoprofen, meclufenamic acid, meloxicam, phenylbutazone, and tolfenamic acid. There are significant differences in product approval and availability depending on the country of interest. Other non-approved NSAIDs



Figure 3 Lateral radiograph of stifle joint of a dog with degenerative joint disease. New bone formation is apparent on many aspects of the stifle joint.



Figure 4 Intra-operative view of the stifle joint illustrated in Figure 3. Note eroded joint surface and new bone formation at bottom right.

that have been recommended to treat OA include aspirin, piroxicam, and a host of human products. Be aware that manufacturers of most of the human products have limited or no data relating to dogs, either with regard to efficacy or a safe dosage range. Furthermore, the majority of reported toxicities with NSAIDs in dogs are related to off-label use of human-approved products.

It is very important for practitioners to remember that the clinical response to a particular drug is quite individualistic. Dogs may respond favorably to one product and not another, so if an NSAID is indicated in a case and the first product used does not achieve a positive clinical response, do not forsake NSAIDs but consider prescribing a different product.

The following is a brief discussion of NSAIDs prescribed for OA in dogs. It is unfortunate that the research on efficacy and safety is not uniform between products. As an example, only carprofen and etodolac have undergone prospective, blinded, large scale clinical evaluation for the treatment of OA in dogs (6–8). The review will start with approved drugs and then be followed by a select group of non-approved drugs. With regard to non-approved drugs, discussion will be reserved for products that have relevant scientific data available in dogs.

Carprofen

Carprofen is an approved NSAID for use in the treatment of OA





Figure 5
Golden Retriever with degenerative joint disease of right elbow. Note the unnatural attitude of the right forelimb.



Figure 6
Lateral radiograph of elbow from dog in Figure 5. Note severe arthritic changes.



Figure 7 *Dorsal-ventral radiograph of a dog with severe hip dysplasia. Note the almost flat acetabulae and span of new bone.*

Table 1
Recommended dosages of the most commonly used NSAIDs

<i>Drug</i>	<i>Recommended dose, frequency, routes</i>
Carprofen	2.2 mg/kg, every 12 hours orally
Etodolac	10–15 mg/kg every 24 hours orally
Ketoprofen	2.0 mg/kg initially, 1.0 mg/kg every 24 hours for subsequent doses orally
Meloxicam	0.2 mg/kg every 24 hours orally
Tolfenamic acid	4.0 mg/kg every 24 hours orally for 3 days only. Repeat following 4 days off drug. Not recommended for chronic administration
Aspirin	10–25 mg/kg every 8 to 12 hours orally
Piroxicam	0.3 mg/kg every 24 hours initially, extend to every 48 hours for chronic dosing

in dogs. It is a member of the arylpropionic acid class of NSAIDs, is a reversible inhibitor of cyclooxygenase, and has been demonstrated to modify cell-mediated immune responses (9, 10). Carprofen has been shown to improve limb function, as measured using both subjective and objective analysis, in clinical trials of dogs with naturally occurring OA (6, 7). Suspected adverse effects associated with carprofen are reported to be near 0.2%, with the majority being GI in nature (6, 7, 11). This data is consistent with the COX-2 selectivity reported for carprofen (12). Recent association with liver dysfunction has been reported and deserves special attention. However, the overall incidence of reports of liver dysfunction was in the order of 0.02% of all dogs treated (11, 13). Limited data on carprofen's effects on cartilage metabolism suggests that these are dose-related and at therapeutic levels cartilage metabolism may not be negatively impacted (14). Additionally, the injectable form of carprofen is now widely used in the management of acute perioperative pain associated with surgery in dogs. A discussion on the use of carprofen and other NSAIDs as analgesics for acute pain is beyond the scope of this article.

Etodolac

Etodolac is a member of the pyranocarboxylic acid class with potent analgesic activity. It has recently been released in the USA for the treatment of OA in the dog (15). Etodolac has been shown to inhibit PGE₂ synthesis by macrophages, but is even more effective in

inhibiting PGE₂ biosynthesis by chondrocytes and synoviocytes (16). Extensive enterohepatic circulation has been reported in the dog, and this maintains serum concentrations for extended periods. A recent clinical trial demonstrated that etodolac was effective in improving rear limb function in dogs with chronic osteoarthritis secondary to hip dysplasia (8). Toxicity studies in dogs found that etodolac has a low potential for gastric ulceration at therapeutic dosages (17, 18). Etodolac has been demonstrated to preferentially inhibit COX-2 (19). When examining potential effects on cartilage metabolism, *in vitro* data provides evidence that etodolac preserves collagen syntheses, but there is conflicting data regarding the effect on proteoglycan synthesis (20–23).

Ketoprofen

Ketoprofen is an arylpropionic acid which is a potent inhibitor of cyclooxygenase (24). It is approved for use in dogs and cats in Europe and Canada (25, 26). Unfortunately there is little peer-reviewed literature available to the clinician regarding the clinical use of this product to treat OA in small animals. The investigation of ketoprofen's effects on cartilage metabolism, like most other products, has primarily utilized *in vitro* studies. The conclusions in all studies was that ketoprofen has no influence on proteoglycan synthesis or collagenase activity in normal or osteoarthritic cartilage (27). Ketoprofen did stimulate proteoglycan synthesis in immature cartilage at low concentrations, however (28, 29). One note for

practitioners in areas where the oral formulation of this product is not available: anecdotal reports suggest that vomiting commonly occurs in dogs when commercial, human, over-the-counter products are used at the recommended dose. As with carprofen, the injectable formulation of ketoprofen is widely used in the management of acute perioperative pain in dogs.

Meclofenamic acid

Meclofenamic acid is an anthranilic acid derivative and a member of the fenamates family. While it is approved for use in dogs in the USA, it has not been evaluated specifically for the treatment of OA. Diarrhea has been described with meclofenamic acid use in dogs and concerns about potential significant adverse GI side effects have been reported (9). Meclofenamic acid is not commonly recommended for use in dogs (5, 25, 26).

Meloxicam

Meloxicam is a member of the oxicam family. Meloxicam is a potent inhibitor of prostaglandin synthesis and exhibits antipyretic and analgesic properties (30). It is approved for use in dogs in Europe. Objective data on efficacy is limited, but recent research models have demonstrated an excellent ability of meloxicam to attenuate the clinical signs of induced synovitis in dogs (31, 32). *In vivo* and *in vitro* data reveal a very favorable COX-2:COX-1 ratio for meloxicam, suggesting it is COX-2 selective (30). Research models have shown potent antiinflammatory activity along with low GI and renal toxicity (30). Effects on cartilage metabolism seem to be minimal. Concentrations of meloxicam which cause pronounced inhibition of prostaglandin production appear to have no effect on cartilage proteoglycan production or the production of certain cytokines likely to be important in cartilage destruction (33, 34). Despite such data, adverse reactions have occurred with meloxicam, emphasizing the point that all NSAIDs, regardless of their safety profiles, are potentially toxic to patients and cannot be given without proper supervision.

Phenylbutazone

Phenylbutazone is a member of the pyrazoles family. Despite being approved for use in the dog, surprisingly little clinical information is available regarding its use and it is not strongly recommended for the treatment of OA in the dog (5, 9, 26, 27). Although thought to be less toxic to dogs than to man (5), phenylbutazone has been associated with blood dyscrasias, GI injury, hepatitis, and nephropathy in dogs and cats (35, 36). The reported dosage for dogs varies dramatically. Despite the lack of objective data on efficacy, a recent survey of Australian veterinarians found phenylbutazone was the preferred treatment for painful or inflammatory musculoskeletal disorders of dogs (37).

Tolfenamic acid

Tolfenamic acid is an anthranilic acid derivative and a member of the fenamates family. It is approved in some countries with a limited therapeutic window. Little objective peer-reviewed data is available on tolfenamic acid in dogs. Specific recommendations on limiting the use of this product reinforce the significant adverse reaction potential of this agent.

Acetylsalicylic acid

Aspirin, while not approved, historically has probably been the most commonly used medication for the treatment of OA in dogs. It is effective, relatively inexpensive, and readily available. The recommended dose of aspirin is 10–25 mg/kg orally every 8 to 12 hours. Subjective evaluation of dogs given aspirin for treatment of OA indicated a dose-related response (5). This response is

recognized with respect to symptom relief but also an increasing frequency of GI toxicity occurs as the dose approaches 25 mg/kg PO every 8 hours. Buffered aspirin has been demonstrated to cause less GI irritation than plain aspirin when administered to dogs (38). Aspirin has been shown to damage both normal and arthritic cartilage by suppressing proteoglycan biosynthesis. However, data strongly suggests that this alteration in glycosaminoglycan metabolism is dependent on the proteoglycan content of the extracellular matrix. This variable is different in each clinical case, thus the extent to which this experimental data can be extrapolated to the clinical situation is limited.

Piroxicam

Piroxicam is a member of the oxicam family of NSAIDs. Piroxicam has an elimination half-life of approximately 40 hours in the dog (39). Based on clinical response and this long elimination half-life, once-daily or once every other day dosing has been successfully used in the dog. Piroxicam has been administered at a dose of 0.3 mg/kg orally once daily for many months for the treatment of canine transitional cell neoplasia. Approximately 18% of patients demonstrated GI toxicity in that study (40). The suggested dose for the treatment of osteoarthritis is 0.3 mg/kg every other day. In a blinded study, gastroendoscopic evaluation of healthy dogs given piroxicam at a dose of 0.3 mg/kg orally once daily for 28 days failed to demonstrate a difference in gastroduodenal lesion development between treated and control dogs (41). Administration of piroxicam to dogs has shown no adverse effects on either normal canine articular cartilage or normal canine chondrocytes. Yet data from *in vitro* studies of piroxicam on human healthy and arthritic chondrocytes found potential detrimental effects. This conflicting data makes interpretation and application of the *in vitro* data to the clinical patient very difficult.

Naproxen

Naproxen is the classic example of the difference between metabolism of an NSAID in humans and dogs (5). The elimination half-life of naproxen in the dog is approximately 72 hours, while in humans it is approximately 14 hours (42, 43). If used, the recommended canine dose is 1.2–2.8 mg/kg once daily (5). The problem with administering naproxen to the dog is that the commonly available human preparation is a 220 mg tablet. A 40 kg dog would require one-quarter of a tablet daily and would be easily overdosed if administered an entire tablet. Due to the narrow margin of safety and reports of GI toxicity with overdose, it is not wise to recommend naproxen for use in dogs.

ADVERSE REACTIONS

The most common problems associated with NSAID administration to dogs involves the GI tract. Some of the GI toxicities associated with NSAID use are believed to be due to inhibition of endogenous prostaglandins. Signs may range from vomiting and diarrhea, including hematemesis and melena, to a silent ulcer that results in perforation. The incidence of GI toxicity in normal or osteoarthritic dogs treated with NSAIDs is unknown. There is evidence to suggest that arthritic animals may be more susceptible to NSAID-induced GI injury than normal animals (44). Recent experience with widespread use of carprofen, meloxicam, and data from humans identifies additional risk factors for GI toxicity.

Concurrent administration of other medications (especially other NSAIDs or corticosteroids)

Previous GI bleeding or the presence of other systemic diseases may contribute to adverse reactions (5, 11). Increased caution must



be taken when prescribing NSAIDs to geriatric patients. Elevated susceptibility to NSAID toxicity in the geriatric patients may be due to decreases in albumin levels, hepatic and renal function and metabolic rate, and changes in the volume of distribution (45, 46). The effect of aging on an individual patient's ability to metabolize NSAIDs is likely to be variable. However, given the potential toxicity of NSAIDs, for these patients it is appropriate to initially dose at the low end of the recommended range and to assess the response critically (5).

Renal dysfunction may occur with NSAID administration as a consequence of prostaglandin inhibition. Renal prostaglandin synthesis is very low under normovolemic conditions. When normovolemia is challenged, prostaglandin synthesis is increased and is important to maintaining renal perfusion (5). NSAID use must be considered very carefully in hypovolemic animals. This is especially important to remember with the increasing use of NSAIDs perioperatively for pain management. Another, perhaps less appreciated area of possible concern, is with working dogs that receive an NSAID before working. Since heavy and prolonged exertion can lead to hypovolemia, and possibly renal compromise, there may be the potential for adverse effects (5).

Minimising adverse reactions

Every effort should be made to prevent, rather than treat the adverse reactions associated with NSAID use. NSAIDs should not be used alone in the management of OA but combined with weight loss, exercise modification and physiotherapy. After an initial continuous dosing schedule, combined with the aforementioned program, one should consider decreasing the NSAID usage after the patient begins to show benefits from the treatment. While chronic use may be necessary, the goal should be to use the minimum amount of drugs to maintain the patient's now-improved function. NSAIDs may also be given on an 'as needed' basis to these improved patients, or initially to less severely affected dogs. It should also be stressed that concurrent use of other NSAIDs or glucocorticoids provides no additional therapeutic benefit but does increase the potential for adverse reactions. Finally, as stressed in the adverse reaction section, as the patient ages or the addition of medications for non-related problems increases, so should the monitoring for potential problems.

FUTURE TRENDS WITH NSAIDS

The future uses of NSAIDs can be broken down into two areas: types of available products and potential uses. The first area will be controlled largely by the pharmaceutical industry in relation to the type and number of products on the market. In general, the near future will see an increase in the number of NSAIDs available to the practitioner. There is also a significant move toward compounds described as COX-2 specific products. In fact, one may see these products no longer listed as NSAIDs but simply classified as COX-2 selective products. Once these show equivalent efficacy to current products, they will become attractive due to their (probable) lower adverse reaction profile. A second group of drugs which may start to enter the market will be products targeting both the cyclooxygenase and lipo-oxygenase pathways, or solely the lipo-oxygenase pathway. Certainly, there is growing evidence that alterations in LTB₄ and other mediators of the lipo-oxygenase pathway can alter the clinical manifestations of OA.

A variety of research areas are being pursued to improve the safety of existing and new NSAIDs. One promising area is coupling NSAIDs to a nitric oxide (NO)-releasing moiety. These NO-NSAIDs inhibit both isoforms of COX with the same potency as the parent NSAID, but they have markedly decreased gastric toxicity (47). Also,

NO-NSAIDs inhibit NO synthase expression, which is unregulated during gastric injury and seems to improve healing of pre-existing acutely induced ulcers. Other novel areas of research include the preassociation of NSAIDs with a zwitterionic phospholipid to prevent interactions between the NSAID and the mucosa (47).

It is entirely possible that the methods of administration of NSAIDs will expand. The use of injectable NSAIDs has dramatically increased in the past few years in the area of perioperative pain relief and also for the relief of acute musculoskeletal dysfunction. There is also increasing data examining the potential use of NSAIDs directly within the CNS and possibly via transdermal application.

Finally, as both the types of products and the potential methods of application increase, expect these drugs to be advocated in areas other than the management of OA. For example, where consistent, safe, pain management is required.

CONCLUSION

With the increased availability of approved NSAIDs to the small animal practitioner, their use will continue to expand in the management of OA in dogs. Proper choice of a product should be based upon available efficacy and safety data, clinical experience and patient response. While safety profiles are much improved, there is still potential for significant adverse reactions, particularly in older animals, those with concurrent systemic diseases, or those on multiple medications (especially glucocorticoids). Judicious use of NSAIDs, as part of your overall management program for OA, can help provide your patients with improved clinical outcomes.

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