Top 5 Situations for Judicious NSAID Use

Natalie Smith, DVM
Claire L. Fellman, DVM, PhD, DACVIM, DACVCP
Cummings School of Veterinary Medicine at Tufts University

NSAIDs are commonly used in veterinary medicine to control pain and inflammation and include COX inhibitors (eg, carprofen, deracoxib) and grapiprant, a newer prostaglandin-receptor antagonist. NSAIDs act by reducing the production or action of proinflammatory prostaglandins and are generally well-tolerated, although potential adverse effects may include GI upset, nephrotoxicity, and hepatotoxicity.

Following are the authors' 5 most common uses of NSAIDs, along with important considerations for patient safety.

TOP 5 SITUATIONS FOR JUDICIOUS NSAID USE

1. Osteoarthritis
2. Management of Postoperative Pain
3. Fever
4. Antineoplastic Therapy
5. Musculoskeletal Injury

1 Osteoarthritis

A common application of NSAIDs is the management of osteoarthritis (OA). Because OA is characterized by both chronic and acute flare-ups of pain and inflammation secondary to joint pathology, the analgesic and anti-inflammatory properties of NSAIDs can be helpful with intermittent or continuous

therapy.[1,2] Numerous NSAIDs (eg, carprofen, meloxicam, firocoxib, deracoxib, grapiprant) are labeled for management of OA in dogs; however, no NSAIDs are currently FDA-approved for long-term use in cats.

Although NSAIDs are typically well-tolerated in veterinary patients, sustained use to treat OA in older patients warrants close monitoring for potential adverse effects in the GI tract, kidneys, and liver. GI adverse effects have been linked to a variety of mechanisms (eg, direct irritation of the GI mucosa, inhibition of prostaglandin E_2) and potentially include ulceration, gastritis, enteritis, and perforation.[3] COX expression in the kidneys can lead to production of prostaglandins, which help maintain renal homeostasis by affecting renal blood flow and glomerular filtration rate, among other functions.[4] Thus, use of NSAIDs in dogs may exacerbate underlying chronic kidney disease or lead to acute kidney injury, reversible renal insufficiency, or papillary necrosis.[5-8]

Adverse effects in the liver are uncommon and can be attributed to idiosyncratic reactions.[9] Hepatopathy has been suggested or documented with NSAID use.[10-15] Idiosyncratic hepatotoxicity that occurs with carprofen administration typically involves acute hepatic necrosis, and signs of toxicosis (eg, marked increase in serum ALT) usually occur ≈2 to 4 weeks after exposure.[11]

COX-1 and COX-2 expression play a major role in maintaining renal blood flow.

OA = osteoarthritis

In patients receiving long-term NSAID therapy, baseline laboratory work, (ie, patient hematocrit, liver enzymes, kidney values, and urinalysis) should be performed to help determine whether the patient has underlying renal or hepatic dysfunction. In addition, ongoing clinical monitoring of renal and hepatic parameters is recommended, and the pet owner should monitor for evidence of GI intolerance (eg, inappetence, vomiting, diarrhea, melena) at home. The authors recommend blood work be rechecked ≈2 to 4 weeks after initiation of NSAID treatment, then every 3 to 6 months. In patients that develop adverse effects while receiving an NSAID, the drug should be stopped and laboratory work (minimum CBC and serum chemistry profile) repeated to assess for possible drug toxicity.

2 Management of Postoperative Pain

NSAIDs are frequently used to provide analgesia during surgical procedures (eg, ovariohysterectomy, fracture repair, mass removal) but are generally contraindicated in patients undergoing GI surgery, as there are risks for ulceration and delayed healing.[16-21] COX-1 and COX-2 expression is increased in inflammatory conditions (eg, those induced during surgery). NSAIDs inhibit COX-1 and COX-2 expression, thus decreasing the production of inflammatory mediators (eg, prostaglandins, thromboxanes) responsible for peripheral and central sensitization to pain stimuli.[3,22]

A primary consideration in patients with postsurgical pain is the timing of NSAID administration in the perioperative period. NSAIDs have been shown to provide better postsurgical analgesia when administered prior to surgery rather than immediately following surgery.[23-30] However, human and veterinary patients have frequently experienced hypotension while under anesthesia, and the kidneys are highly vulnerable to hypotensive insult.[31] COX-1 and COX-2 expression play a major role in maintaining renal blood flow, particularly during hypotension, and preoperative inhibition of COX expression by NSAIDs may contribute to postoperative renal dysfunction.[32] Several studies

evaluating renal function after NSAID administration as anesthesia have not found evidence of significant dysfunction; however, these studies primarily included young, healthy dogs, with the oldest being 89 months of age.[24-26,33,34] Accordingly, preoperative use of NSAIDs may be reasonable in healthy patients that do not have underlying renal disease or increased risk for hypotensive events; blood pressure monitoring is recommended in patients under anesthesia. Because patients with existing renal disease may be at increased risk for hypotensive events, NSAIDs as anesthesia should not be used in these patients.

3 Fever

NSAIDs are also used to provide clinical relief from fever, as their antipyretic effects are mediated by central and peripheral thermoregulatory mechanisms. The primary antipyretic action decreases prostaglandin E_2 levels in the hypothalamus by inhibiting COX.[35] Fever at sites of tissue inflammation is reduced via suppression of pyrogenic cytokines, increased release of endogenous antipyretics and anti-inflammatory molecules, and decreased adhesion molecule expression to reduce endothelial cell interactions with leukocytes.[35] This can allow NSAIDs to rapidly reduce fever, potentially controlling life-threatening febrile reactions and significantly improving patient comfort.

NSAIDs should be used with caution in patients with fever of unknown origin, especially in cases in which infectious disease has not been ruled out or immune-mediated disease is likely.

OA = osteoarthritis

Although NSAIDs are effective at reducing fever, they usually do not treat the underlying cause. Resolution of a low- to moderate-grade fever can indicate the appropriate treatment is being used (eg, antimicrobials for system infection, glucocorticoids for immune-mediated polyarthritis). Patients with fever of unknown origin that were referred for further diagnostics and given NSAIDs, glucocorticoids, or antibiotics within 24 hours of presentation had significantly prolonged time to diagnosis as compared with patients not treated within this period.[36] In addition, pyrogenic fever is a protective mechanism in patients with sepsis or fungal infections. A mild febrile response in humans with pyrogenic fever secondary to infection has been shown to improve clinical outcomes.[37] Thus, NSAIDs should be used with caution in patients with fever of unknown origin, especially in cases in which infectious disease has not been ruled out or immune-mediated disease is likely; treatment with glucocorticoids may be indicated.

4 Antineoplastic Therapy

NSAIDs used in conjunction with metronomic chemotherapy are important in the management of cancer patients and can be used as a single-agent treatment for some tumors.[38-40] For metronomic chemotherapy, conventional oral cytotoxic chemotherapy agents can be given at relatively low doses and regular intervals (eg, every 24-48 hours) over a sustained period. Metronomic chemotherapy agents are often delivered with other agents (eg, NSAIDs, small-molecule inhibitors).[38] Therapy is aimed at altering tumor microenvironment, primarily via antiangiogenic mechanisms, rather than directly targeting the tumor cells. COX-2 inhibition via NSAIDs can decrease cell proliferation, reduce production of proangiogenic factors (eg, vascular endothelial growth factor), and increase the rate of apoptosis.[39] Adjuvant metronomic chemotherapy has been explored in a variety of tumor types (eg, hemangiosarcoma, soft tissue sarcoma) and can safely be incorporated in treatment regimens for cancer patients.[38]

Carcinomas (eg, urothelial carcinoma, mammary carcinoma, nasal adenocarcinoma, anal sac adenocarcinoma) express COX-2.[40-43] NSAIDs have activity against canine urothelial carcinoma, with several different COX inhibitors (eg, piroxicam, deracoxib, firocoxib) reported.[44-46] NSAIDs may be recommended as part of standard therapy for carcinomas because of their potential antitumor activity and ability to provide analgesia. One study reported a median survival time of 181 days in dogs with urothelial carcinoma treated with piroxicam alone as compared with 291 days in dogs treated with piroxicam in combination with mitoxantrone.[46] Single-agent NSAIDs may be more effective when combined with conventional chemotherapy agents for treatment of urothelial carcinoma but can be used alone when conventional chemotherapy is not possible.

The effectiveness of NSAIDs for antineoplastic therapy should be balanced against possible adverse effects. GI adverse effects may limit the use of NSAIDs, especially in patients also being treated with conventional chemotherapy agents or small-molecule inhibitors that may independently cause GI adverse effects. NSAIDs should not be used concurrently with glucocorticoids, which are often used in the treatment of round cell neoplasias (eg, lymphoma, mast cell tumors). Owners of patients treated with NSAIDs as part of antineoplastic therapy should be advised to monitor for signs of GI adverse effects. Baseline and follow-up laboratory work is also recommended (as described for OA; see ***Osteoarthritis***, page 64).

5 Musculoskeletal Injury

NSAIDs are also frequently used in patients with acute musculoskeletal injuries. Pain associated with acute injuries persists during both the inflammatory and healing phases and may last up to 3 months before being considered chronic.[17] During the inflammatory phase, prostaglandin expression may increase up to 80-fold, making COX inhibition a valuable target for therapeutic intervention.[47]

Patients with acute musculoskeletal injuries are typically given shorter courses of NSAID therapy, reducing the risk for potential adverse effects in the kidneys, GI tract, and liver, as compared with patients given sustained NSAID therapy. However, caution is recommended in patients with pre-existing GI disease, and screening for renal or hepatic dysfunction should be done prior to NSAID administration, especially in older patients.

Conclusion

NSAIDs are important therapeutics because of their ability to reduce inflammation and provide effective analgesia. With appropriate monitoring for GI, renal, and hepatic adverse effects, NSAIDs can be used safely to treat a variety of conditions in small animal patients.

References

1. Innes JF, Clayton J, Lascelles BDX. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. *Vet Rec*. 2010;166(8):226-230.
2. Bennett D, Zainal Ariffin SM, Johnston P. Osteoarthritis in the cat: 2. how should it be managed and treated? *J Feline Med Surg*. 2012;14(1):76-84.
3. KuKanich B, Bidgood T, Knesl O. Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs. *Vet Anaesth Analg*. 2012;39(1):69-90.
4. Lomas AL, Grauer GF. The renal effects of NSAIDs in dogs. *J Am Anim Hosp Assoc*. 2015;51(3):197-203.
5. Raekallio MR, Hielm-Björkman AK, Kejonen J, Salonen HM, Sankari SM. Evaluation of adverse effects of long-term orally administered carprofen in dogs. *J Am Vet Med Assoc*. 2006;228(6):876-880.
6. Knapp DW, Richardson RC, Chan TC, et al. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med*. 1994;8(4):273-278.
7. Roberts ES, Van Lare KA, Marable BR, Salminen WF. Safety and tolerability of 3-week and 6-month dosing of Deramaxx (deracoxib) chewable tablets in dogs. *J Vet Pharmacol Ther*. 2009;32(4):329-337.
8. Silverman LR, Khan KN. "Have you seen this?" Nonsteroidal anti-inflammatory drug-induced renal papillary necrosis in a dog. *Toxicol Pathol*. 1999;27(2):244-245.
9. Monteiro-Steagall BP, Steagall PVM Lascelles BDX. Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. *J Vet Intern Med*. 2013;27(5):1011-1019.
10. Trepanier LA. Idiosyncratic drug toxicity affecting the liver, skin, and bone marrow in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2013;43(5):1055-1066.
11. MacPhail CM, Lappin MR, Meyer DJ, et al. Hepatocellular toxicosis

associated with administration of carprofen in 21 dogs. *J Am Vet Med Assoc*. 1998;212(12):1895-1901.
12. Metacam (meloxicam oral suspension) [product label]. Duluth, GA: Boehringer Ingelheim Animal Health; 2019.
13. Deramaxx (deracoxib) chewable tablets [product label]. Greenfield, IN: Elanco; 2010.
14. Previcox (firocoxib) chewable tablets [product label]. Duluth, GA: Merial; 2015.
15. Onsior (robenacoxib) injection [product label]. Greenfield, IN: Elanco; 2010.
16. Berry SH. Analgesia in the perioperative period. *Vet Clin North Am Small Anim Pract*. 2015;45(5):1013-1027.
17. Epstein M, Rodan I, Griffenhagen G, et al. 2015 AAHA/AAFP Pain Management Guidelines for dogs and cats. *J Am Anim Hosp Assoc*. 2015;51(2):67-84.
18. Friton G, Thompson C, Karadzovska D, King S, King JN. Efficacy and safety of injectable robenacoxib for the treatment of pain associated with soft tissue surgery in dogs. *J Vet Intern Med*. 2017;31(3):832-841.
19. Bienhoff SE, Smith ES, Roycroft LM, Roberts ES. Efficacy and safety of deracoxib for control of postoperative pain and inflammation associated with soft tissue surgery in dogs. *Vet Surg*. 2012;41(3):336-344.
20. Rushfeldt CF, Sveinbjørnsson B, Søreide K, Vonen B. Risk of anastomotic leakage with use of NSAIDs after gastrointestinal surgery. *Int J Colorectal Dis*. 2011;26(12):1501-1509.
21. Goodman L, Torres B, Punke J, et al. Effects of firocoxib and tepoxalin on healing in a canine gastric mucosal injury model. *J Vet Intern Med*. 2009;23(1):56-62.
22. Vuilleumier PH, Schliessbach J, Curatolo M. Current evidence for central analgesic effects of NSAIDs: an overview of the literature. *Minerva Anestesiol*. 2018;84(7):865-870.
23. Lascelles BD, Cripps PJ, Jones A, Waterman-Pearson AE. Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Vet Surg*. 1998;27(6):568-582.
24. Crandell DE, Mathews KA, Dyson DH. Effect of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation. *Am J Vet Res*. 2004;65(10):1384-1390.
25. Boström IM, Nyman GC, Lord PE, Häggström J, Jones BE, Bohlin HP. Effects of carprofen on renal function and results of serum biochemical and hematologic analyses in anesthetized dogs that had low blood pressure during anesthesia. *Am J Vet Res*. 2002;63(5):712-721.
26. Ko JC, Miyabiyashi T, Mandsager RE, Heaton-Jones TG, Mauragis DF. Renal effects of carprofen administered to healthy dogs anesthetized with propofol and isoflurane. *J Am Vet Med Assoc*. 2000;217(3):346-349.
27. Welsh EM, Nolan AM, Reid J. Beneficial effects of administering carprofen before surgery in dogs. *Vet Rec*. 1997;141(10):251-253.
28. Gramke HF, Petry JJJ, Durieux ME, et al. Sublingual piroxicam for postoperative analgesia: preoperative versus postoperative administration: a randomized, double-blind study. *Anesth Analg*. 2006;102(3):755-758.
29. Nakayama M, Ichinose H, Yamamoto S, Nakabayashi K, Satoh O, Namiki A. Perioperative intravenous flurbiprofen reduces postoperative pain after abdominal hysterectomy. *Can J Anaesth*. 2001;48(3):234-237.
30. Norman PH, Daley MD, Lindsey RW. Preemptive analgesic effects of ketorolac in ankle fracture surgery. *Anesthesiology*. 2001;94(4):599-603.
31. Domi R, Huti G, Sula H, et al. From pre-existing renal failure to perioperative renal protection: the anesthesiologist's dilemmas. *Anesth Pain Med*. 2016;6(3):e32386.
32. Murrell J. Perioperative use of non-steroidal anti-inflammatory drugs in cats and dogs. *In Pract*. 2018;40:314-325.
33. Boström IM, Nyman G, Hoppe A, Lord P. Effects of meloxicam on renal function in dogs with hypotension during anaesthesia. *Vet Anaesth Analg*. 2006;33(1):62-69.
34. Frendin JH, Boström IM, Kampa N, Eksell P, Häggström JU, Nyman GC. Effects of carprofen on renal function during medetomidine-propofol-isoflurane anesthesia in dogs. *Am J Vet Res*. 2006;67(12):1967-1973.
35. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. *Am J Med*. 2001;111(4):304-315.
36. Battersby IA, Murphy KF, Tasker S, Papasouliotis K. Retrospective study of fever in dogs: laboratory testing, diagnoses and influence of prior treatment. *J Small Anim Pract*. 2006;47(7):370-376.
37. Walter EJ, Hanna-Jumma S, Carraretto M, Forni L. The pathophysiological basis and consequences of fever. *Crit Care*. 2016;20(1):200.
38. Gaspar TB, Henriques J, Marconato L, Queiroga FL. The use of low-dose metronomic chemotherapy in dogs-insight into a modern cancer field. *Vet Comp Oncol*. 2018;16(1):2-11.
39. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. *Nat Rev Cancer*. 2004;4(6):423-436.
40. Cancedda S, Sabattini S, Bettini G, et al. Combination of radiation therapy and firocoxib for the treatment of canine nasal carcinoma. *Vet Radiol Ultrasound*. 2015;56(3):335-343.
41. Knottenbelt C, Mellor D, Nixon C, Thompson H, Argyle DJ. Cohort study of COX-1 and COX-2 expression in canine rectal and bladder tumours. *J Small Anim Pract*. 2006;47(4):196-200.
42. Knudsen CS, Williams A, Brearley MJ, Demetriou JL. COX-2 expression in canine anal sac adenocarcinomas and in non-neoplastic canine anal sacs. *Vet J*. 2013;197(3):782-787.
43. Millanta F, Asproni P, Canale A, Citi S, Poli A. COX-2, mPGES-1 and EP2 receptor immunohistochemical expression in canine and feline malignant mammary tumours. *Vet Comp Oncol*. 2016;14(3):270-280.
44. McMillan SK, Boria P, Moore GE, Widmer WR, Bonney PL, Knapp DW. Antitumor effects of deracoxib treatment in 26 dogs with transitional cell carcinoma of the urinary bladder. *J Am Vet Med Assoc*. 2011;239(8):1084-1089.
45. Knapp DW, Henry CJ, Widmer WR, et al. Randomized trial of cisplatin versus firocoxib versus cisplatin/firocoxib in dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med*. 2013;27(1):126-133.
46. Henry CJ, McCaw DL, Turnquist SE, et al. Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive urinary bladder carcinoma. *Clin Cancer Res*. 2003;9(2):906-911.
47. Hertel J. The role of nonsteroidal anti-inflammatory drugs in the treatment of acute soft tissue injuries. *J Athl Train*. 1997;32(4):350-358.