NSAIDs and Beyond:

The POWER of NSAIDs in the Multimodal Management of Canine Osteoarthritis

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Introduction

For many years, pain was managed by administration of a single pharmacological agent (if it was managed at all), and often only when the animal "proved" to the clinician that it was suffering. Within the past 10 – 15 years advancements in the understanding of pain physiology, introduction of more efficacious and safe drugs, and the maturation of ethics toward animals have considerably improved the management of pain veterinary patients need and deserve.

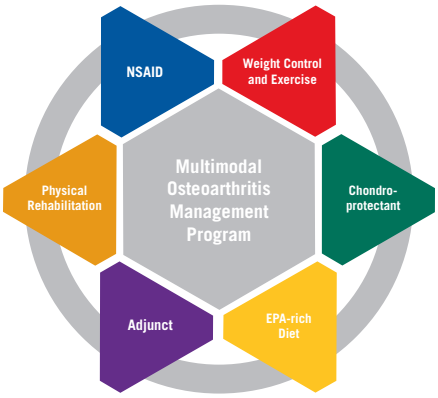

Figure 1. Multimodal management of osteoarthritis includes a combination of medical and non-medical modalities.

Following the lead in human medicine, veterinarians have come to appreciate that the network of pain processing involves an incredibly large number of transmitters and receptors, all with different mechanisms, dynamics and modes of action. From this appreciation comes the conclusion that it is naive to expect analgesia with a single agent, working by a single mode of action. Multimodal analgesia was initially understood as the administration of a **combination** of drugs from different pharmalogical classes each having different, non-competing modes of action. However the concept has further expanded to include differing methods of delivery, e.g., oral, systemic, transdermal, transbuccal, and epidural as well as non-pharmacologic modalities such as acupuncture and physical rehabilitation. Central to the concept is that combinations will be synergistic (or at least additive), requiring a reduced amount of each individual drug, and therefore less potential for adverse response to medication. Selection of drugs within the "cocktail" would be optimal if they collectively blocked all four of the physiologic processes associated with pain recognition (i.e., transduction, transmission, modulation and perception).

Perioperative multimodal analgesia is widely practiced today in veterinary medicine, however monotherapy continues to be common practice for managing the chronic pain of osteoarthritis (OA). NSAIDs are the foundation for treating OA, and are likely to remain so for some years to come. Many clinicians manage the elusive pain of OA by sequencing different NSAIDs until satisfactory patient results are achieved or unacceptable adverse reactions are experienced. However, optimal clinical results are more frequently obtained by implementing a multimodal protocol for osteoarthritis (Figure 1).

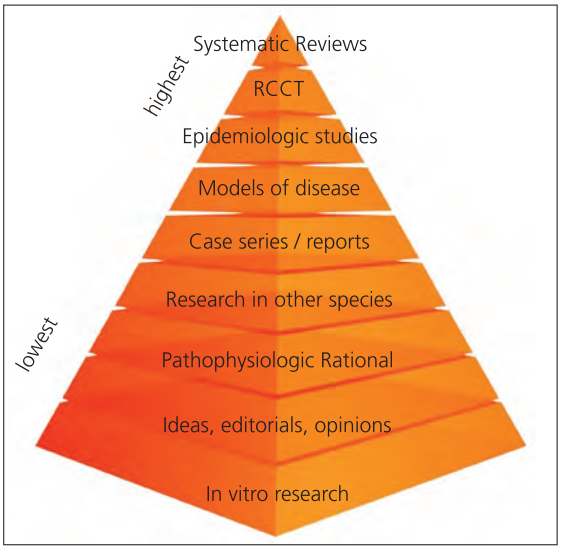

Figure 2. Evidence Pyramid. The hierarchy of evidence is based on the concept of causation and control of bias.

Quality of Evidence

Although contemporary experience precedes published literature, there is a growing evidence-base for the multimodal management of OA.

Quality of evidence is an important consideration when making a therapeutic decision, and can be graded from 1 to 4 (Figure 2). Grades 1 and 2 compose the highest level of evidence, consisting of systematic reviews (meta-analyses) and well designed properly randomized, controlled,

patient-centered clinical trials (RCCT). Grade 3 notes a moderate level of evidence, consisting of well-designed, non-randomized clinical trials, epidemiological studies (cohort, case-control), models of disease and dramatic results in uncontrolled studies. Grade 4 is the lower level of evidence encompassing expert opinions, descriptive studies, studies in non-target species, pathophysiologic findings and in vitro studies. Very few reports have been made reviewing the quality of evidence of treatments for osteoarthritis in dogs.[1]

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are the fastest growing class of drugs in both human and veterinary medicine. This reflects their broad use as anti-inflammatory agents, analgesics and antipyretics. As with antibiotics, NSAIDs can be considered to have been introduced in successive generations to date: 1) first generation, i.e., aspirin, phenylbutazone, meclofenamic acid, 2) second generation, i.e., carprofen, etodolac, meloxicam, and 3) third generation, i.e., tepoxalin, deracoxib and firocoxib. However, unlike the logic of "saving the big gun antibiotic" for last, so as to avoid microbial superinfections, logic would dictate using the optimal NSAID at the earliest opportunity, so as to avoid the physiologic complication of "windup."

Currently, several NSAIDs (aspirin, carprofen, cinchophen, deracoxib, etodolac, firocoxib, flunixin, ketoprofen, meloxicam, phenylbutazone, tepoxalin, tolfenamic acid and vedaprofen) have approval for the control of canine perioperative and/or chronic pain in various countries. NSAIDs approved for feline use are far more limited (meloxicam, tolfenamic acid, ketoprofen, carprofen and aspirin) in various countries for short term administration.

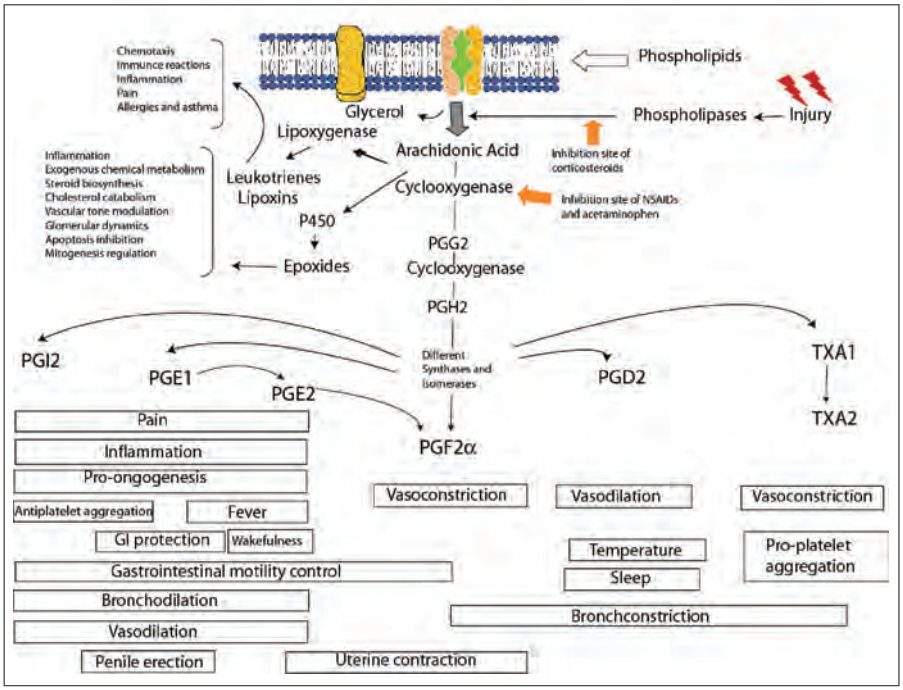

Figure 3. The arachidonic acid pathway generates a variety of eicosanoids that influence various physiologic functions.

Arachidonic Acid Pathway

In most respects NSAIDs can be characterized as a class, although there are molecule-specific characteristics among individual drugs. NSAIDs manifest their mode of action in the arachidonic acid (AA) cascade (Figure 3).

Arachidonic acid is a ubiquitous substrate derived from the continual degradation of cell membranes. Arachidonic acid is metabolized to various eicosanoids via the cyclooxygenase (COX) pathway to prostaglandins or via the lipoxygenase (LOX) pathway to leukotrienes. Under the influence of local tissues, these end-product prostanoids can be pro-inflammatory and enhance disease processes and pain.

It is important to note that the function of many prostanoids is tissue-dependent, e.g., prostaglandins may contribute to pain and

inflammation in the arthritic joint, while they enhance normal homeostatic functions of vascularization, bicarbonate and mucous secretion in the GI tract.

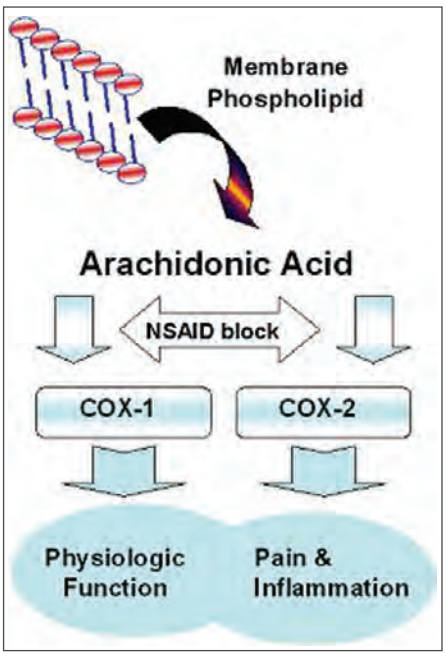

Figure 4. COX-1-mediated prostaglandins tend to be associated with constitutive physiologic functions, while COX-2-mediated prostaglandins tend to be associated with pain and inflammation.

At one time it was believed that blocking the cyclooxygenase pathway would lead to a build up of the substrate AA, resulting in increased production of leukotrienes. This has been refuted by some,[2] while supported by others.[3] Because corticosteroids have their mode of action at a location higher in the arachidonic cascade than NSAIDs, it is redundant to use them concurrently, and doing so markedly increases the severity of adverse reactions.[4-6] Data from humans show that the risk of NSAID-induced gastrointestinal complications are doubled when a NSAID is used concurrently with a corticosteroid.[7]

Cyclooxygenase (COX) Isozymes

Approximately 20 years following discovery of the arachidonic acid pathway as the mode of action for NSAIDs, it was discovered that the cyclooxygenase enzyme exists as at least two isoenzymes: COX-1 and COX-2.[8,9] These two distinct COX isoforms have been identified as products of two separate genes.[10] Initially COX-1-mediated prostaglandins were thought to be constitutive physiologically, and should be retained, while COX-2-mediated prostaglandins were pathologic and should be eliminated for the control of inflammation and pain. (Figure 4) COX-2-selective NSAIDs were designed for this purpose — the selective suppression of COX-2-mediated prostaglandins.

In contrast to COX-1, COX-2 is not widely expressed under normal physiologic conditions, but is up-regulated in cells such as synoviocytes, fibroblasts, monocytes, and macrophages under the influence of proinflammatory mediators. Both isoforms are membrane-bound glycoproteins found in the endoplasmic reticulum and, particularly COX-2, in the nuclear envelope of the cell. The overall amino acid sequence of COX-1 and COX-2 is similar. In humans, the only difference between the two isoforms is a single nucleotide in the active site region. The isoleucine residue in COX-1 is replaced by a valine residue in COX-2. This single difference has been shown to have a marked effect on the overall size and shape of the binding site, apparently the basis for COX-2-inhibitor selectivity (Figure 5 a,b).

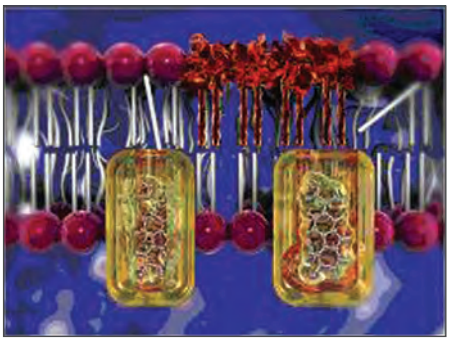

Figure 5 a. The COX-2 site has a larger entry port and a characteristic side-pocket. Small, traditional NSAIDs fit into both sites, blocking both COX-1 and COX-2-mediated prostaglandin production from arachidonic acid, hence the term *non-selective* NSAID.

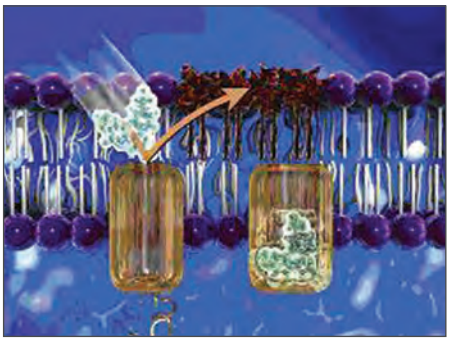

Figure 5 b. Coxib-class NSAIDs were designed to be too large for the COX-1 receptor site; however, they fit hand-in-glove within the COX-2 receptor site. These drugs spare COX-1-mediated prostaglandin production and block COX-2-mediated prostaglandin production, i.e., they are COX-1-*sparing* and COX-2-*selective*.

The IC_{50} is defined as the concentration of drug (NSAID) needed to inhibit the activity of cyclooxygenase by 50%. In keeping with the above rationale, one would like to have a high concentration of NSAID before causing 50% inhibition of COX-1 ("good guy") and a low concentration of NSAID to reach the IC_{50} for COX-2 ("bad guy"):

IC_{50} of COX-1 (good)	HIGH
IC_{50} of COX-2 (bad)	LOW

The higher the numerator and lower the denominator, the higher the absolute value. Therefore, a greater COX-1/COX-2 ratio theoretically suggests a more optimal performing NSAID. With this in mind, pharmaceutical companies began designing NSAIDs that inhibit COX-2 at low concentrations, but only inhibit COX-1 at high concentrations. Many factors such as species, incubation time and enzyme source can influence the data obtained from studies designed to evaluate this ratio. Additionally, when measuring COX-2 potency, the kinetics of inhibition are very complex and time dependent. Consequently, different values have been reported for the same drug. Although COX-1:COX-2 ratios vary by investigators, relative ratio standings provide insight as to a drug's expected species-specific cyclooxygenase activity (Table 1). Complicating this issue, some report ratios of COX-2/COX-1 rather than the more conventional COX-1/COX-2.

Drug	***Ratio of IC_{50} COX-1/ COX-2[a]***	***Ratio of IC_{50} COX-1/ COX-2[b]***	***Ratio of IC_{50} COX-1/ COX-2[c]***	***Ratio of IC_{50} COX-1/ COX-2[d]***
Meloxicam	12.2	10	10	
Carprofen	1.8	9	16.8	5
Ketoprofen	0.4	6.5	.02	
Aspirin			0.4	
Celecoxib				6.2
Deracoxib				36.5
Firicoxib				155

Table 1. Canine COX-1:COX2 ratios reported by different investigators [a]Kay-Mugford P, et al. *Am J Vet Res.* 2000 Jul;61(7):802-10. [b]Brideau C, Van Staden C, Chan CC. *Am J Vet Res.* 2001 Nov;62(11):1755-60. [c]Streppa HK, Jones CJ, Budsberg SC. *Am J Vet Res.* 2002 Jan;63(1):91-4. [d]Li J, Lynch MP, Demello KL, et al. *Bioorg Med Chem.* 2005 Mar 1;13(5):1805-9.

COX-1:COX-2 Ratios of Contemporary Veterinary NSAIDs

It has been suggested that a COX-1/COX-2 ratio of <1 would be considered COX-1-*selective*, a ratio >1 as COX-2-*preferential*, a ratio >100 as COX-2-*selective* and a ratio >1,000 as COX-2-*specific*. Selectivity nomenclature is used loosely and such comparative ranking has not been associated with clinical correlation. Hence, most all discussions of COX data presented by pharmaceutical manufacturers include the disclaimer, "clinical relevance undetermined," because the data is sourced *in vitro*.

We now know that the "good guy COX-1," "bad guy COX-2" approach is naive, recognizing that COX-2 is needed constitutively for reproduction, central nervous system nociception, renal function and gastrointestinal lesion repair. In fact, the physiologic functions associated with cyclooxygenase activity overlap.

Accordingly, there is likely a limit as to how COX-2-selective an NSAID can be without causing problems, e.g., inhibiting endogenous repair of a gastric lesion. This limit is not known. More important than how COX-2-selective an NSAID might be is whether or not the NSAID is COX-1-sparing, i.e., preserving homeostatic physiology. Further, it is logical to avoid a COX-1-selective NSAID (ratio <1) peri-operatively, so as not to enhance bleeding. The coxib-class NSAIDs, with their high COX ratio and COX-1-sparing feature, have been shown to be associated with less risk for GI complications in human studies.[11]

NSAID Safety

Comparative safety of NSAIDs in dogs is difficult to determine. The incidence of adverse events for a specific NSAID is determined by dividing the number of new events within a specified period of time by the population of dogs receiving the drug. Since not all adverse drug events are reported and not all reported events are directly causal and the total number of dogs receiving a particular drug at any given time is unknown, accurate comparative data are unobtainable. Accordingly, most NSAID manufacturers can state with credibility, "no NSAID has been proved safer than (fill in the blank)." Nevertheless, all ADEs should be reported to the FDA and drug manufacturer so that general trends can be tracked and documented.

Adverse drug event reports at the United States Food and Drug Administration Center for Veterinary Medicine provide some insights as to why ADEs from NSAID use might be so high:

- 23% of pet owners state that veterinarians never discuss adverse effects of the medication
- 22% of pet owners state they are not given client information sheets about the prescribed drugs which are provided by pharmaceutical companies for the purpose of pet owner education
- 14% of prescribed NSAIDs are dispensed in other than original packaging, thereby denying pet owners drug information provided on the label
- Only 4% of pet patients prescribed drugs are given pre-administration blood analyses

As a class of drug, NSAIDs are most commonly associated with adverse reactions to the gastrointestinal (GI) tract (64%), renal system (21%) and liver (14%), respectively (Table 2).[12] There is no published information on similar feline adverse drug events. Gastrointestinal problems associated with NSAIDs can be as benign as regurgitation or as serious as gastric ulceration and perforation. Vomiting has been identified as the most frequent clinical sign associated with gastric perforation. Pet owners should be informed that while taking an NSAID, if their pet experiences vomiting, the drug should be discontinued and the patient promptly examined.

Drug	*Vomiting*	*Diarrhea*
Carprofen	3.1% (3.8)	3.1% (3.8)
Etodolac	4.3% (1.7)	2.6% (1.7)
Deracoxib	2.9% (3.8)	2.9% (1.9)
Tepoxalin	2.0% (4.8) at 7 days 19.6% at 28 days	4.0% (0) at 7 days 21.5% at 28 days
Meloxicam	25.5% (15.4)	12.1% (7.4)
Firocoxib	3.9% (6.6)	0.8% (8.3)

Table 2. GI Adverse Events Reported in Clinical Trials (values represent mean of test article [placebo]) Data sourced from drug inserts. Caution should be used in comparing adverse events among different drugs because of differences in study populations, data collection methods and reporting methods.

NSAID-associated Gastrointestinal Ulceration

Gastric perforations are most frequently found near the pyloric antrum of the stomach and have a poor prognosis if not discovered early and treated aggressively. Risk factors identified with NSAID-associated gastric ulceration are most commonly seen with inappropriate use: 1) overdosing, 2) concurrent use of multiple NSAIDs, and 3) concurrent use of NSAIDs with corticosteroids.

Lascelles et al[6] observed that 23/29 GI perforations in an NSAID retrospective review

occurred in the area of the pyloric antrum. Reasons for this anatomical focus being at higher risk include speculation that it is subject to recurrent bathing by bile reflux through the pylorus. Apart from a few studies that have examined the effect of NSAIDs on gastric mucosal production of prostanoids.[13-15] COX-selectivity has largely been determined using *in vitro* assays, and assumptions have been made about gastrointestinal effects based on these *in vitro* data. Given the variability in results from *in vitro* assays, and the lack of understanding of COX physiology in the canine proximal GI tract, making assumptions about the clinical effects of various NSAIDs based on *in vitro* data may lead to erroneous conclusions.

Wooten et al[16] reported an assessment of the *in vitro* action of NSAIDs in the region of the gastrointestinal tract which appears to be at greatest risk for ulceration in the dog. Prostaglandin levels were found to be significantly higher in the pylorus than in the duodenum, which may be explained by differences in COX expression in the pylorus versus the duodenum, where the need for protection from refluxed bile is high. The "more traditional" NSAIDs (aspirin and carprofen) decreased the total concentration of prostaglandins in the gastric mucosa, while prostaglandin levels were not altered by the coxib-class NSAID (deracoxib).

To date, the only study assessing the association between a selective COX-2 inhibitor (deracoxib) and gastroduodenal perforation revealed that in most cases (26/29) were associated with an inappropriately high dose, or concurrent administration with other NSAIDs or corticosteroid, or rapid switching (<24 hours) from one NSAID to another.[6] These findings suggests that when GI perforation occurs following administration of a selective COX-2 inhibitor, other factors, such as over-dosing, concurrent administration of drugs inhibiting prostanoid production or rapid change from one NSAID to another play a major role in the production of ulceration. This is corroborated by documentation that 75%-80% of all ADE reports with deracoxib use are associated with inappropriate use.[17]

NSAIDs and Kidney Function

Through regulation of vascular tone, blood flow, ion and water balance and rennin, prostaglandins are important for normal kidney function.[18] In situations of decreased systemic blood pressure or circulating blood volume, prostaglandins regulate and maintain renal blood flow.[19] Both the COX-1 and the COX-2 isoforms are expressed in the kidneys of dogs, rats, monkeys and humans where they both play constitutive roles.

Therefore, at recommended dosing, no one NSAID is safer than another with regard to kidney function in these species. NSAID drug complications of hypovolemia and hypotension have led to acute renal failure and death in both dogs and cats.[20] Information regarding COX-1 and COX-2 distribution or expression under varying conditions of the feline kidney is unknown. Meloxicam is, perhaps, the most frequently administered NSAID in cats, and repeated use (off-label) has been associated with acute renal failure in cats. The manufacturer cautions against such repeated use.

BUN and creatinine elevations occur relatively late in kidney disease, therefore screening urine for protein has been suggested for early disease detection.

Any positive screening result should be followed by measurement of urine protein:creatinine ratio for a more complete assessment. Any patient with compromised renal function is at risk with any NSAID administration, particularly when under-hydrated.

NSAIDs and Liver Function

Drug-induced *hepatopathy* (defined as an elevation of liver enzyme values) is a rare, but potentially serious adverse consequence of several drug classes including NSAIDs, volatile anesthetics, antibiotics, antihypertensives and anticonvulsants. In comparison idiosyncratic *hepatotoxicosis* is the rare (estimated 0.02% incidence[21]) potentially lethal liver toxicity of carprofen. This hepatotoxicosis does not appear to be associated with dose or duration of administration, and no epidemiological study has shown the hepatotoxicosis to be breed-related. A hypothesis for carprofen-related hepatotoxicosis is that reactive acyl glucuronide metabolites are generated that can covalently bind and heptenize hepatocyte proteins, thereby promoting an immunological response in the liver.[22-24]

It is well advised to characterize liver enzymes before and during NSAID administration, especially when an NSAID is being administered long-term. However, an increase in liver enzymes is difficult to interpret, as any chronic drug administration can cause an elevation, and liver enzymes are not a good measure of hepatic function. When liver enzymes are elevated and concern for liver function is present, liver function tests should be performed. Mere elevation of liver enzymes may not be cause for discontinuing an NSAID.

Aspirin

Aspirin presents unique risk factors to the canine patient. Aspirin is both topically and systemically toxic (even at low doses of 5-10 mg/kg SID), chondro-destructive, causes irreversible platelet acetylation, and is associated with GI bleeding.[25,26] The American Medical Association (AMA) reports that 16,500 people die each year associated with NSAID toxicity,[27] with an over-representation of aspirin. Pet owners often consider aspirin benign because it is available over-the-counter (OTC) and the media suggests it is safe. Even low-dose aspirin has consistently been associated with GI petechiation and hemorrhage. Aspirin does not have a US Food and Drug Administration (FDA) license for use in the dog, and the plasma concentrations regarded as being therapeutic are relatively close to the toxic levels.[28] In theory, since aspirin causes GI lesions, it would be inappropriate to sequentially progress from aspirin to a strongly COX-2 selective NSAID (which might restrict the COX-2 necessary for repair) without an adequate washout period following the aspirin. It is also perilous to use aspirin together with another NSAID or corticosteroid.

Standard formulations of buffered aspirin have not been shown to sufficiently neutralize gastric acid or prevent mucosal injury.[29] Enteric-coated aspirin causes less gastric injury in humans but absorption is quite variable[30,31] with coated tablets having been observed to pass in the feces.

Potential for increased GI damage from the concurrent use of aspirin with another NSAID resides with the Aspirin Triggered Lipoxin (ATL) pathway. ATL is a protective mechanism that is blocked with the concurrent administration of another NSAID,

giving rise to an alternative pathway for arachidonic acid metabolism that actually enhances the potential for aspirin toxicity.

Anti-ulcer Agents

One goal of anti-ulcer treatment is to lower intragastric acidity so as to prevent further destruction of the GI tract mucosa. Cimetadine (Tagamet®), a histamine, H_2-receptor blocker, is commonly used. Cimetidine requires dosing 3 to 4 times daily, however it is not effective in preventing NSAID-induced gastric ulceration. Omeprazole (Prilosec®) is a substituted benzimidazole that acts by inhibiting the hydrogen-potassium ATPase (proton pump inhibitor) that is responsible for production of hydrogen ions in the parietal cell. It is 5 to 10 times more potent than cimetadine for inhibiting gastric acid secretion and has a long duration of action, requiring once-a-day administration. It may be useful in decreasing gastric hyperacidity, but has minimal effect on ulcer healing. Misoprostol (Cytotec®) is a synthetic prostaglandin E_1 analog used to prevent gastric ulceration. It decreases gastric acid secretion, increases bicarbonate and mucus secretion, increases epithelial cell turnover and increases mucosal blood flow. Both cimetadine and misoprostol require dosing 3 to 4 times daily and adverse reactions mimic those of gastritis and ulcerations (Table 3).

Group	***Generic name***	***Brand name***	***Dose***
Proton pump inhibitors (PPI)	Omeprazole	Prilosec	Canine: 0.7 mg/kg, PO
	Lansoprazole	PrevAcid	
	Rabeprazole	AcipHex	
	Pantoprazole	Protonix	
	Esomeprazole	Nexium	
Prostaglandin analog	Misoprostol	Cytotec	Canine: 2-5 mg/kg, tid, PO
H_2 blockers	Cimetidine	Tagamet	Canine/Feline: 10 mg/kg, tid, PO, IV, IM Feline: 3.5 mg/kg, bid, PO or 2.5 mg/kg, bid, IV
	Ranitidine	Zantac	Canine: 2 mg/kg, tid, PO, IV
	Famotidine	Pepcid	Canine/Feline: 0.5 mg/kg, sid, PO, IV, IM,, SQ or 0.25 mg/kg, bid, PO, IV, IM, SQ
	Nizatidine	Axid	Canine: 2.5-5 mg/kg, sid, PO
Mucosal sealant	Sucralfate	Carafate	Canine: 0.5-1 g, tid-bid, PO Feline: 0.25 g, tid-bid, PO

Table 3. Pharmacologic Agents for NSAID GI Prophylaxis and Treatment

Washout

Washout between NSAIDs is poorly researched, however one survey report suggests that failure to implement a washout between different NSAIDs may put the patient at risk for GI pathology. One must consider the reason for changing NSAIDs when considering a washout period. If the reason for change is efficacy, in the healthy dog "washout" is a lesser issue than if the reason for change is intolerance. With intolerance, a minimal washout time should be no less than the time required to recover from adverse clinical signs. Most agree that washout following aspirin is a unique scenario, due in part to the phenomena of Aspirin Triggered Lipoxin (ATL).[32] Five to seven days washout following aspirin is probably adequate. One study has

been conducted where injectable carprofen was followed at the next SID dosing with deracoxib.[33] In this study of a limited number of healthy dogs, no difference was noted in following injectable carprofen with either oral carprofen or oral deracoxib. Pain relief during a washout period can be obtained by the use of other class drugs, e.g., acetaminophen, tramadol, amantadine, gabapentin or opioids.

Enhancing Responsible NSAID Use

Every pet owner who is discharged with medication, including NSAIDs, should have the following questions addressed:

1. What is the medication supposed to do?
2. What is the proper dose and dosing interval?
3. What potential adverse response(s) are possible?
4. What should I do if I observe an adverse response?

Both verbal and written instructions should be given. Pre-administrative urinalysis and blood chemistries are well advised prior to dispensing NSAIDs for two reasons. First, the pet may be a poor candidate for any NSAID, i.e., it may be azotemic or have decreased liver function. These physiologic compromises may not preclude the use of NSAIDs, but such a determination must be justified. Second, a baseline status should be established for subsequent comparison, should the patient show clinical signs suggestive of drug intolerance. For the patient on a long-term NSAID protocol, the frequency of laboratory profiling should be determined by clinical signs and age. Minimal effective dose should always be the therapeutic objective, and routine examinations constitute the practice of good medicine. Since alanine aminotransferase (ALT) is more specific than serum alkaline phosphatase (SAP) for liver status, an elevation of ALT 3-4 times laboratory normal should prompt liver function tests. Because the kidney expresses both COX isozymes constitutively, no one NSAID can be presumed safer than another for kidney function, and any patient that is hypotensive or insufficiently hydrated is not a good candidate for NSAID administration.

NSAIDs play a major role in a perioperative protocol for healthy animals, due to their features as antiinflammatories, analgesics and anti-pyretics. NSAID inclusion helps prevent CNS "wind up" and provides synergism with opioids.[34] Surgery cannot be performed without resultant iatrogenic inflammation, and the best time to administer the anti-inflammatory drug is preemptively — before the surgery. It is imperative that surgical patients be sufficiently hydrated if NSAIDs are used perioperatively. Under the influence of gaseous anesthesia, kidney tissue may suffer from under-perfusion, at which point prostaglandins are recruited to assist with this perfusion, and if the patient is under the influence of an anti-prostaglandin (NSAID), kidney function may compromised. In human medicine, some suggest that NSAIDs should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment.[35]

Efficacy

Measuring ground reaction forces is the most common way to objectively assess weight bearing in dogs. Using a force plate platform, investigators can compare, with certainty, the degree of lameness over a period of time. In its simplest terms,

force plate gait analysis measures ground reaction forces that result when a dog places its limb during a specific gait. Typically, peak force in the vertical axis (z peak) is used to objectively measure limb function. A relative rank of NSAID efficacy or pain relief for can be generated by comparing the z peak of the affected limb.

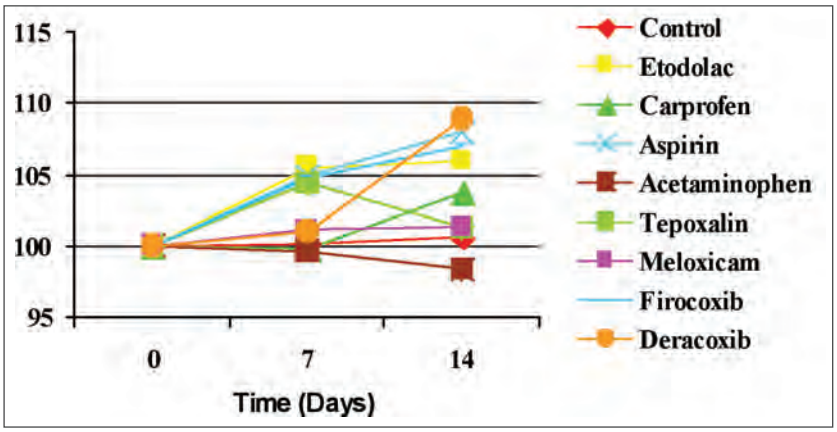

Figure 6. Comparative efficacy of contemporary NSAIDs used in veterinary medicine. Adapted from Millis DL. A Multimodal approach to treating osteoarthritis. 2006 Western Veterinary Conference Symposium Proceedings.

Force plate gait analysis in an orthopedic model has become the standard for ranking NSAID efficacy in canids on an objective basis.[36] Although several NSAID manufacturers have made public their studies comparing one or two products, none have compared the large group of NSAIDs most commonly used in clinical practice (Table 4). Dr. Darryl Millis and colleagues at the University of Tennessee reported such a study,[37] conducted independent of commercial support, using the force plate gait analysis (Figure 6).

Drug	***Primary Assessment Method***	***Ground Reaction Force Assessment***
Carprofen	Subjective owner and veterinary assessment indicated improvement more likely in treated dogs	No significant difference between placebo dogs and treated dogs
Etodolac	Ground reaction forces	Peak vertical force improved 0.4%, 2.3% and 1.6% with placebo, low-dose, and high-dose treatments, respectively. Vertical impulse improved 0.4%, 0.13%, and 0.22%, respectively
Deracoxib	Ground reaction forces	Peak vertical force improved 7.4% with treatment vs. placebo. Vertical impulse improved 4.9% with treatment compared with placebo
Tepoxalin	Subjective changes compared with carprofen, no placebo comparison. Subjective improvement similar to carprofen	Not measured
Meloxicam	Subjective assessment of lameness, weight bearing, pain on palpation, and overall improvement compared with placebo. Significant improvement noted on Day 14 of one 14-day study. Significant improvement noted in the parameter of overall assessment on Day 7 by veterinary assessors and on Day 14 by owners in a second study	Not measured
Firocoxib	Subjective comparison to etodolac. No comparison to placebo. Subjective efficacy comparable to etodolac.	Ground reaction forces were determined in a subset of patients. Results were comparable between firocoxib and etodolac.

Table 4. Comparison of NSAID Efficacy Studies Used for US FDA Approval

Objective measurement of lameness severity in cats is quite difficult, as cats do not comply with force plate protocols. However, pressure mats have been used to reveal the distribution of pressures associated with paw contact.[38] Use of the pressure mat to evaluate lameness in cats will likely see further development. The use of acceleration-based activity monitors may also allow for objective measurement of improved mobility following treatment for osteoarthritic conditions in the cat.[39]

NSAID Administration

Time of Administration

Timing of once daily administration is a common question; should the drug be administered in the morning or in the evening? Some argue that morning administration is most logical, taking advantage of C_{max} during that time of the day when the dog might be most active. Others suggest the NSAID should be dosed so that C_{max} is reached to ensure maximal rest for the animal; proposing that the animal performs best following a good night's rest. There is no consensus.

With or Without Food

Many of the contemporary NSAIDs are labeled for use either with or without food. Administration with food takes advantage of the increased production of gastric bicarbonate and associated buffering. Feeding an NSAID together with food may enhance acceptability in some dogs. Concurrent administration of any medication with food increases the risk of creating food aversions. Cats are particularly sensitive to this phenomena.

NSAID Compatibility With Other Agents

NSAIDs are highly protein bound and may compete with binding of other highly protein bound drugs, particularly in the hypoproteinimic animal, resulting in altered drug concentrations. Fortunately, the number of other highly protein bound drugs is minimal. A variety of drugs and agents may be influenced by the concurrent administration of NSAIDs (Table 5).

Drug	***NSAIDs may increase the toxicity of***	***NSAIDs may decrease the efficacy of***	***NSAID toxicity may be increased by***
Classical NSAIDs (clinically significant COX-1 inhibition)	Warfarin, methotrexate, valproic acid, midazolam, furosemide, spironolactone, sulfonylureas, heparin	Furosemide, thiazide, ACE inhibitors, ß blockers	Aminoglycosides, furosemide, cyclosporine (renal), glucocorticoids (GI), heparin, gingko, garlic, ginger, ginseng (hemorrhage)
Coxibs and relatively COX-2 selective agents	Warfarin, methotrexate, valproic acid, midazolam, furosemide, spkironolactone, sulfonylureas	Furosemide, thiazides, ACE inhibitors, ß blockers	Aminoglycosides, furosemide, cyclosporine (renal), glucocorticoids (GI)
Phenylbutazone, acetaminophen	Warfarin, sulfolureas		Phenobarbital, alcohol, rifampin, metoclopramide

Table 5. NSAIDs: Potential Drug Interactions adapted from Trepanier LA. Potential interactions between non-steroidal anti-inflammatory drugs and other drugs. *J Vet Emergency and Critical Care* 2005; 15(4): 248-253.

Because many owners self medicate their pets with "natural" products, some of which can potentially influence the concurrent use of a NSAID, it is well advised to ask owners for a complete listing of everything they are giving their pet per os (Table 6).

Herb	***Interacting Drugs***	***Results***
St. John's wort	Cyclosporine, fexofenadine, midazolam, digoxin, tacrolimus, amitriptyline, warfarin, theophylline	Decreased plasma drug concentrations
Gingko	Warfarin, heparin, NSAIDs, omeprazole	Bleeding Decreased plasma concentrations
Ginseng	Warfarin, heparin, NSAIDs, opioids	Bleeding Falsely elevated serum digoxin levels (laboratory test interaction with ginseng) Decreased analgesic effect (laboratory test interaction with ginseng)
Garlic, chamomile ginger	Warfarin, heparin, NSAIDs	Bleeding

Table 6. Potential Herb-Drug Interactions adapted from Goodman L, Trepanier L. Potential drug interactions with dietary supplements. Compendium (SAP) October 2005, 780-789

Cats and NSAIDs

There are approximately 69 million cats in the USA[40] and approximately 10 million in the UK.[41] Radiographically detectable degenerative joint disease is reported in 90% of cats over 12 years of age.[42] Efficacy of NSAIDs for relief of chronic pain in the cat is difficult to demonstrate, but empirically embraced. Probable reasons for the relative void of evidence-base for NSAIDs in cats include:

- Assumption by pharmaceutical manufacturers that the market for cat analgesics is not financially rewarding
- Difficulty of identifying pain in cats, and therefore indications for administration
- Scarcity of information about NSAIDs in cats
- Potential risk of NSAID toxicity in cats

Salicylate toxicity in cats is well established. Cats present a unique susceptibility for NSAID toxicity because of slow clearance and dose-dependent elimination. Cats have a low capacity for hepatic glucuronidation of NSAIDs,[43] which is the major mechanism of metabolism and excretion for this class of drugs. Acetaminophen toxicity in cats results in methemaglobinemia, liver failure and death. **Cats are particularly susceptible to acetaminophen toxicity** due, in part, to defective conjugation of the drug and conversion to a reactive electrolytic metabolite. Because of its delivery form as an elixir, meloxicam is sometimes used preferentially in small dogs and cats. However, only carprofen injectable and meloxicam injectable are approved for use in the cat (country dependent) and manufacturers stress ***one-time dosing only***. There are no data to support the safe, chronic use of NSAIDs in cats. The manufacturer of meloxicam has recommended reducing the original approval dose from 0.2 to 0.1 mg/kg because of potential gastrointestimal problems. This suggests particular attention be given to accurate dosing of small dogs and cats. As with all NSAIDs in dogs or cats, potentially causal gastric ulcerations have been observed.

Looking to the Future

NSAIDs are the fastest growing class of drugs in both human and veterinary medicine because of their relatively safe resolution of a wide range of pathological conditions. Based upon current understanding of their mode of action, future NSAIDs will likely **not** be developed to be "stronger-longer," i.e., supremely COX-2 selective, with a very long half-life. Instead, NSAID development may well offer species- and/or disease-specific molecules, increased safety profiles and augmenting benefits such as nitrous oxide inhibition. At present this class of drug offers immense benefits, constrained most often only by issues of safe, responsible use.

Improving Safety

The following guidelines can be used to minimize risk factors for NSAID ADEs:

1. Proper dosing
2. Administer minimal effective dose
3. Dispense in approved packaging together with owner information sheets
4. Avoid concurrent use of multiple NSAIDs and NSAIDs with corticosteroids
5. Refrain from use of aspirin
6. Provide pet owners with both oral and written instructions for responsible NSAID use
7. Conduct appropriate patient chemistry/urine profiling. Do not use in patients with reduced cardiac output or in patients with overt renal disease.
8. Conduct routine checkups and chemistry profiles for patients on chronic NSAID regimens. Do not fill NSAID prescriptions without conducting patient examinations
9. Caution pet owners regarding supplementation with over-the-counter NSAIDs
10. Administer gastrointestinal protectants for high at-risk patients on NSAIDs
11. Avoid NSAID administration in puppies and pregnant animals
12. NSAIDs may decrease the action of ACE inhibitors and furosemide, a consideration for patients being treated for cardiovascular disease
13. Geriatric animals are more likely to be treated with NSAIDs on a chronic schedule, therefore their "polypharmacy" protocols and potentially compromised drug clearance should be considered.
14. Provide sufficient hydration to surgery patients administered NSAIDs
15. Report ADEs to the product manufacturers

Summary

Nonsteroidal anti-inflammatory drugs have changed the practice of both human and veterinary medicine. Their utilization will likely continue for decades to come as we learn more specific applications and features of these molecules. As with all medications, adverse reactions from NSAIDs are possible, however the benefits far outweigh problems associated with their use. With responsible use of NSAIDs, we must always strive for the minimal effective dose, within established dosing ranges, and assess the benefit:risk ratio for each individual patient.

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