SAFE USE OF NSAIDS IN DOGS **CANCER PAIN MANAGEMENT**

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This session is designed to help practicing veterinarians safely prescribe non-steroidal anti-inflammatory drugs (NSAIDs). Despite their widespread clinical use and familiarity, adverse effects and toxicity can occur, and veterinarians often avoid using NSAIDs. Fortunately, most of these side effects can be avoided, or at least minimized, with careful practice and good client communication.

The ultimate goal of this lecture is to convince practitioners that many patients will greatly benefit from NSAID use, including in ways that may not be obvious or in situations where their use might be typically avoided. Careful planning, communication, and monitoring can greatly reduce risk and adverse effects. When toxicity does occur, there are strategies that can successfully reduce the impact on our patients.

Non-steroidal Anti-inflammatory Drugs as a Class

NSAIDs are a chemically diverse class of drugs that all block cyclooxygenase (also called prostaglandin synthase or COX), which is the enzyme responsible for the formations of the prostaglandins, prostacyclins, and thromboxane. These cytokines have broad constitutive roles besides being mediators of inflammation and pain. Their efficacy as analgesics has traditionally been thought to be due to prostaglandin inhibition.

Despite NSAIDs common inhibition of this enzyme, they use substantially different mechanisms of action to achieve this action. These differences affect enzyme specificity, pharmacokinetics, and, in some cases, toxicity. There is ever-evolving information on the role that COX specificity has on efficacy and safety of this class of drugs. There is also evidence that COX physiology is quite species-specific and much more complex than previously thought. One interesting complexity of NSAID pharmacology is that the anti-inflammatory and analgesic effects last longer than plasma half-lives would predict. Some NSAIDs take advantage of this and have built-in specificity for protein binding in inflamed tissue.

The Benefits of NSAID Use

Although we commonly focus on NSAIDs used as analgesics in acute pain, they have other, less obvious benefits. One of the least appreciated is that early use of NSAIDs with trauma and/or perioperatively can help prevent the development of chronic pain states and persistent post-surgical or traumatic pain syndromes. Untreated or inadequately treated acute, inflammatory pain is a major and controllable risk factor for the development of chronic pain. There is increasing evidence that long term use of NSAIDs in treatment plans for chronic pain can reverse central sensitization and allow for reduction in analgesic use over time. Veterinarians have the potential to greatly impact their patient's future comfort and quality of life by aggressively treating inflammatory pain.

Appropriate Patient Selection for NSAID Use

Ideally, patients should have known normal organ function, are euhydrated and have normal vascular volume, have normal water intake, normal appetite, and normal eliminations. Obviously, these conditions may not be met for many of our sick patients. The art of NSAID use is in assessing risks for complications and relative contraindications.

Basic contraindications for use are:

- Active vomiting or diarrhea
- Known GI ulceration
- Dehydration
- Pre-existing renal or hepatic dysfunction
- Known conditions that pose potential for immediate organ dysfunction (i.e., sepsis, heart failure)
- Concurrent or recent use of other NSAIDs or corticosteroids
- <12 weeks of age

Some of these contraindications should be strictly held. Dogs with active GI disease and those recently receiving other NSAIDs or corticosteroids are at an increased risk of GI ulceration. Puppies younger than 12 weeks of age do

not have fully matured renal protective mechanisms and can have permanent renal damage from NSAID use, although some authors believe that after eight weeks of age the risks are minimal with a single dose or short course.

Dogs with pre-existing hepatic and/or renal dysfunction are at greater risk from adverse effects due to reduced excretion and disruption of normal protective mechanisms. NSAIDs are primarily excreted through hepatic metabolism with some renal involvement. The decision to use NSAIDs in patients with known renal or hepatic dysfunction must be made only when owners are willing to accept the known risks in exchange for benefits in patients suffering without NSAIDs. The details of assessing this risk and prescribing tips for this patient population will be discussed in part II of this session.

Initial NSAID Drug Selection and Dosing Strategies

Due to the narrow therapeutic index of NSAIDs in dogs and the known toxicities, use of an NSAID that is FDA approved for dogs is important. In particular, aspirin is known to cause gastric lesions in virtually 100% of dogs when given at published doses. Despite the well-publicized risk of GI ulceration in FDA approved NSAIDs, this risk is still considerably less than with aspirin.

All approved NSAIDs for dogs have very similar statistical rates and proportions of GI, renal, and hepatic toxicity. Because of this and the lack of clear data demonstrating greater analgesic efficacy of a particular NSAID, the initial choice of a particular drug can be made using factors that improve compliance or convenience. An NSAID that a dog has tolerated in the past is often a good first choice. Because of the wide variety in formulations, sizes, and palatability, pick a drug after consultation with the owner to help insure compliance.

NSAIDs can often be dosed as "to effect" drugs when used long term for chronic pain, but usually require full daily dosing at the beginning of therapy, when pain is at its peak. Consider label doses and dosing intervals as the maximum dose to minimize risk. If relative contraindications to use are present, consider reducing the initial dose and/or increasing the dose interval.

Veterinarians frequently prescribe courses that are too short to adequately reduce inflammation or for the expected duration of pain. Presumably, this is due to either fear of adverse effects with longer courses or discomfort with assessing pain. NSAIDs, like any analgesic, must be given as long as the patient shows signs of pain regardless of our expectation of the time course for resolution of the problem. If we cannot assess pain or owners cannot, then we can at least use the anthropomorphic approach to estimating how long a given problem with cause pain for (i.e., how long would a person with this problem feel pain). In cases where we are attempting to prevent persistent, chronic pain syndromes, this is particularly important.

NSAIDs and Client Communication Necessities

Although the bulk of this session concerns assessing and minimizing the risk of NSAID adverse events, risk is still present when these drugs are prescribed. Because of this, well-informed clients, given specific information about risk, are fundamental to reducing those risks. Compliance surveys of pet owners reveal surprising rates of non-prescription NSAID administration to dogs, alarmingly often without a veterinarian's knowledge. When questioned, pet owners may not understand the basic facts of NSAID use, including that anti-inflammatory medication is analgesic or even why an NSAID was prescribed for their dog. They often have knowledge of NSAID risks, but this is frequently clouded by anecdotal misinformation gleaned from internet "research." Ask, more than once, whether the dog is receiving any other oral or topical medication, any over-the-counter (OTC) medication, or has been prescribed medication by another veterinarian. Owners may tell technicians this information, but not veterinarians, so have multiple staff members ask the question. Sometimes it is helpful to explain to clients that they are putting their dog at risk for significant toxicity by combining medications without medical advice.

Client communication fundamentals before prescribing:

- Explain why an NSAID is being prescribed and its intended effect.
- Explicitly state the known risks.
- Inform owners that dogs are more likely than people to develop GI toxicity from NSAIDs, especially if multiple types are given concurrently.
- Describe why you believe the benefits outweigh the risks in this specific patient.
- Advise owners of their pivotal role in reducing the risk.

- Provide clear instructions for what to do in the case of suspected adverse events.
- Outline a plan for drug monitoring if NSAIDs are to be used chronically.

All of this information should be given to a client verbally, so they can ask clarifying questions. Follow up the discussion with written information. There are excellent written resources available that can be provided to clients. Both AAHA and the FDA have free, downloadable handouts (see suggested resources) for client use, as do several of the NSAID manufacturers.

Clients should be clearly instructed to:

- Only give the medication when the appetite is normal and after the pet has eaten.
- Monitor their pet for loss of appetite, vomiting, or any change in stool color or consistency.
- Discontinue use if they see any of these signs and contact the prescriber.

All of this information should also be on the medication label.

Clients often ask for gastroprotective strategies when using NSAIDs, but there is no data to guide this practice. The only factor known to reduce risk is to only administer NSAIDs when an appetite is present and there is food in the stomach.

Toxicity and Adverse Effects of NSAIDs in Dogs
Potential targets for adverse effects of NSAIDs include:

- GI tract
- Kidney
- Liver
- Coagulation system
- Articular cartilage
- Bone healing
- Adverse drug-drug interactions

These tissues and processes are targets for impact because cyclooxygenase is present in a constitutive role and can become induced or up-regulated in many disease processes. The impacts on coagulation, bone healing, and articular cartilage are rarely clinical reported problems in dogs. There is little data on any of these three problems in dogs with currently FDA-approved NSAIDs, but recent studies have been published on coagulation effects. No clinically relevant changes in thrombosis were found in one comparison study.

As mentioned earlier, as a group and when taken individually, all approved NSAIDs have similar rates and ratios of reported adverse effects. Pet owners often are aware of NSAIDs reported toxicity, but, as we know, large amounts of misinformation circulate regarding the specifics. The relative frequency of GI adverse events is about 64%, about 21% for renal adverse events, and about 14% for hepatic toxicity.

NSAID Drug Monitoring and Management of Adverse Effects
For patients being prescribed short courses of NSAIDs, with little chance of the course being extended to more than 10–14 days, baseline laboratory testing is often skipped. In patients with known risk factors for adverse events, or concurrent illness other than simple trauma or elective surgery, baseline testing is prudent. Knowledge of a minimum data base including at least hematocrit (HCT), total solids (TS), blood urea nitrogen (BUN), creatinine (CR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and urine specific gravity will greatly assist in assessing risk. Even with short term use, owners should be counseled on signs of adverse events.

For patients expected to be on longer courses of NSAIDs, recent baseline testing consisting of CBC, chemistry profile, and urinalysis should be mandatory. Without this information, risk assessment is incomplete and NSAIDs should not be prescribed until this information is obtained. Patients with incidental mild alkaline phosphatase (ALP) elevations are unlikely to have significant reduction in liver function. If liver enzyme elevations are multiple or

moderate-to-severe, then liver function testing (i.e., bile acids) should be performed before considering chronic NSAID therapy.

After NSAID therapy is started, lab work should be rechecked after three to four weeks of therapy to catch subclinical idiosyncratic hepatoxicity or GI ulceration (both of which can occur with any approved NSAID). At minimum, a HCT/TS and chemistry profile should be checked. The author also rechecks at least a liver profile six to eight weeks later to screen for idiosyncratic hepatotoxicity, which usually occurs within the first 90 days of treatment. If all of the lab work is normal, or at least does not show signs of toxicity, then full lab work should be checked every six months of therapy thereafter.

If screening lab work at three to four weeks or six to eight weeks after initiating therapy shows new or worsening elevations in liver enzymes and/or total bilirubin, idiosyncratic hepatotoxicity should be presumed to be cautious. NSAID therapy should be stopped and lab work should be rechecked in another three to four weeks. If the patient is ill or has an elevated total bilirubin, then full investigation and treatment of significant toxicity should be initiated. Patients with idiosyncratic toxicity (and normal liver function prior to initiating therapy) generally have normalizations in liver enzymes within three to four weeks. If they are clinically normal, therapy can be reinitiated with a different NSAID when liver enzymes return to baseline. These reactions should be reported to the FDA and the manufacturer.

If screening lab work reveals new elevations in creatinine or BUN compared to baseline (even if still within the normal range), therapy should be ceased while other possible causes are explored with a urinalysis and urine culture at minimum. If no other cause is identified, then lab work should be rechecked in one to two weeks to monitor progression of azotemia. Resumption of therapy is dependent upon all of these factors and is considerably riskier in the face of known kidney dysfunction.

Patients who become ill while on NSAIDs should have full lab work rechecked as the signs of NSAID toxicity are non-specific. This is particularly important because GI ulceration may remain subclinical in dogs until it is severe.

If any clinical signs *or* lab results are indicative of GI ulceration (vomiting and/or melena, declining HCT/TS, elevated BUN), then NSAID therapy should immediately cease and appropriate therapy instituted. Humans and possibly dogs may develop tolerance (adaptation) to mild gastritis induced by NSAIDs after a short period of use, but this is a different, less dangerous phenomenon than GI ulceration.

Hepatic Adverse Effects of NSAIDs

Hepatic toxicity is a frequent target of misinformation, probably due to pet owners' confusion between inducible hepatotoxicity and idiosyncratic hepatotoxicity. Additionally, many veterinarians and pet owners believe that NSAIDs cause a cumulative toxicity. There is no evidence to support this belief.

Subclinical liver diseases, like chronic active hepatitis, occur regularly in dogs and are a major reason why pre-treatment screening is necessary. Because liver enzyme levels do not directly represent liver *function*, incidental findings of elevated liver enzymes require a more thorough diagnostic process to assess risk of NSAID toxicity. In patients with reduced liver function, their ability to metabolize NSAIDs is impaired. Because liver dysfunction causes risk of GI ulceration, this risk is greatly increased when NSAIDs are administered to these patients.

Learning about and educating clients about idiosyncratic hepatotoxicity of NSAIDs is an important part of safe NSAID use. Although this has been most widely reported with carprofen use, it has been reported with all NSAIDs. This is a rare event; an unpredictable, aberrant immunological response. It is not dose-related and there are no known risk factors. It usually occurs within 90 days of the start of therapy, but can occur at any time. If it is diagnosed when subclinical and baseline liver function was normal, then the toxicity is usually reversible if the drug is withdrawn. This can be fatal or lead to significant, permanent dysfunction if diagnosed when the patient is already sick. Even though it is rare, this condition prompts much of the drug monitoring strategies mentioned earlier.

Renal Adverse Effects of NSAIDs

Prostaglandin E_2 is important in the maintenance of renal perfusion during hypovolemia. Since NSAIDs generally inhibit prostaglandin production, this renal protective effect can be reduced or lost with use of NSAIDs. Although renal toxicity is an important consideration with the use of NSAIDs, no adverse effects on renal function are

expected with long-term use in patients who have normal blood pressure, vascular volume status, and sodium levels. Risk factors for toxicity include high dose NSAIDs, sodium depletion, hypotension, hypovolemia, and anesthesia. Despite this, appropriate anesthetic management, with maintenance of appropriate blood pressure, poses a very low risk for renal toxicity. Patients with hepatic and renal dysfunction with impaired excretion will be at risk for renal adverse effects because toxicity is associated with accumulation of drug in the renal tubules, not COX selectivity.

Transitioning Between NSAIDs or Between Corticosteroids and NSAIDs

There are clinical situations where it is necessary to switch NSAIDs or transition between corticosteroids and NSAIDs. There is little data to guide this practice since plasma half-lives donot adequately predict the persistence of these drugs in tissue, particularly in damaged end-organ tissue. Compared to other NSAIDs, aspirin does irreversibly inactivate platelet function, so it is prudent to wait seven days (long enough for platelets to regenerate) after stopping aspirin before starting other NSAIDs. Beyond this, guidelines are based strictly on anecdotal information.

The recommendations usually distinguish between switching due to adverse effects compared to switching for increased efficacy. A useful guideline is to wait until the clinical signs of the adverse effect have resolved long enough for the affected tissue or organ system to have normalized. An example of this is waiting until vomiting, diarrhea, and appetite have been normal for at least five days before restarting therapy, with a different drug. Conservative estimates for washout periods when with adverse effects range from five to seven days. In some patients, shorter washout times may be tolerated or the clinical situation may dictate rapid transitions. There is evidence that transitioning between NSAIDs and corticosteroids is riskier (for GI toxicity) and that there is increased risk of GI ulceration if NSAIDs are switched without any washout period.

For many patients, rescue analgesics will be needed during washout periods. In patients who have been on chronic NSAID therapy though, the analgesic effects may persist for longer than a week. This often prompts clients to suspect that the NSAIDs were not effective, when, in reality, this is probably more a reflection of their persistence in tissue longer than plasma.

Sensible Guidelines for Safe NSAID Use and Adverse Effect Prevention

- Prescribe only FDA approved NSAIDs with known safety profiles in dogs.
- Educate your clients and staff verbally and in writing about safe NSAID use and common adverse effects.
- Don't combine different NSAIDs or NSAIDs with corticosteroids in any form.
- Remember that washout periods are defined for plasma only.
- Do not use NSAIDs in dogs with pre-existing GI disease or known GI compromise.
- Consider label doses and dosing intervals as maximum doses.
- Pre-treatment and regularly scheduled drug monitoring will catch most toxicity early.
- Only prescribe enough medication to treat until the next scheduled monitoring.
- Instruct owners to only administer NSAIDs with food and when the pet is eating.
- Remind clients at every contact with your hospital to discontinue use and notify the prescriber if their dog has signs of illness when NSAIDs are being administered.

Suggested Reading

Curry, Stephen L., Steven M. Cogar, and James L. Cook. 2005. "Nonsteroidal Antiinflammatory Drugs: A Review". Journal of the American Animal Hospital Association 41: 298-309.

Innes, J.F., J.Clayton, and B.D.X. Lascelles. 2012. "Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis". Veterinary Record 166:226-230.

Khan, Safdar A. and Mark Kay McLean. 2012. "Toxicology of Frequently Encountered Nonsteroidal Anti-Inflammatory Drugs in Dogs and Cats". Veterinary Clinics Small Animals 42:289-306.

KuKanich, Butch, Tara Bidgood and Oliver Knesl. 2012. "Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs". Veterinary Anaesthesia and Analgesia 39:69-90.

Papich, Mark G. 2008. "An Update on Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Small Animals". Veterinary Clincs Small Animals 38:1243-1266.

"What you should know about your pet's pain medication" downloadable client handout: http://www.aahanet.org/PublicDocuments/NSAIDsInfo.pdf

FDA information for clients:
http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm
FDA brochure for clients (downloadable) “Treating Pain in Your Dog”:
http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm196295.htm