Safe and Effective NSAID Use in the Dog

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By
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What happens in a veterinary pain clinic?

- Outpatient chronic pain clinic
- Perioperative pain management
- Management of traumatic and severe pain in hospital patients
Why is the safe use of NSAIDs the goal of this lecture?

Because fear of adverse effects appears to be the reason veterinarians avoid their use.

Learning objectives:

- Understand the short term and long-term benefits of therapy with NSAIDs.
- Recognize important indications for use of NSAIDs.
- Select patients suitable for NSAID therapy.
- Choose a formulation, dose and dose interval.
- Educate pet owners about safe NSAID use.
- Make a reasonable plan for individual drug monitoring.
- Reduce common, preventable adverse events.
- List the different types of commonly seen toxicities and relative frequency.
- Distinguish inducible vs. idiosyncratic drug reactions.
- Recognize and treat side effects as they occur.

Non-steroidal anti-inflammatory drugs are:

- NSAIDs or NSAIAs
- Analgesics
- Antipyretic
- Chemical compounds that block cyclooxygenase
- Suspected of having anti-inflammatory effects separate from cyclooxygenase inhibition
- Highly bioavailable and highly protein bound
- NOT acetaminophen
Benefits of NSAID Use

- Fever reduction
- Acute pain relief
- Chronic pain relief
- Anti-neoplastic effects
- Anti-thrombotic effects

NSAIDs are the most effective treatment for inflammatory pain

Including degenerative joint disease!

Inflammatory Pain

- The most common type of pain, includes:
  - Traumatic
  - Surgical
- Can be somatic or visceral
- OA pain is inflammatory pain but non-neutrophil mediated
Long term benefits of NSAID use for chronic musculoskeletal pain

- Decrease inflammation
- Decrease in central sensitization?
- Decreased pain
- Decrease in activity of endogenous analgesic system
- Increased ability to exercise
- Increased muscle mass

Why are veterinarians so reluctant to use NSAIDs?

- Fear of side effects
  - Pervasive idea of cumulative toxicity
  - Idiosyncratic toxicity potential
- Need for monitoring
  - Is baseline testing necessary?
  - Uncertainty of ideal intervals for monitoring
- Need for client education
  - Requires time to communicate
  - Are written instructions necessary?
- Cost
  - Perception that cost:benefit ratio of prescription NSAIDs is unfavorable

Do you hesitate to use NSAIDs to treat pain even when you don’t have good alternatives?
Consequences of untreated pain

- Increased sympathetic drive
  - Increased cardiac work and myocardial oxygen consumption
- Increased stress hormone response
  - Hypercoagulability
  - Impaired healing
  - Decreased immune function
- Sensitization of:
  - Peripheral nociceptors
  - Central pain pathways

Poorly treated acute pain is a major risk factor for the development of chronic pain

NSAID Patient Selection

- Pick patients with:
  - Normal organ function
  - A normal appetite and normal eliminations
  - Known volume status
  - Acute, inflammatory pain
  - Chronic pain
  - Fevers of known origin that would benefit from lowering
  - Neoplasia, use as part of a combination treatment
NSAID Patient Selection

- Avoid NSAID use in patients with:
  - Vomiting or diarrhea
  - Known GI ulceration
  - Dehydration
  - Pre-existing kidney or hepatic dysfunction
  - Potential for immediate organ dysfunction
  - Concurrent or recent use of other NSAIDs, corticosteroids
  - Ages under 12 weeks

Choosing an NSAID

- Pick:
  - A formulation licensed for use in dogs
  - A preparation that is likely to improve compliance
  - The drug that makes sense for the patient’s weight

Choosing an NSAID

- Consider:
  - Past history of NSAID use in this particular patient
  - That there is no data that shows one formulation is clearly more effective than another
  - Whether this dog has a historically “sensitive stomach”
  - What concurrent medications the patient is being given
  - How long the patient is expected to require NSAIDs
Initial Dosing of NSAIDs

- Consider label doses
- Maximum doses
- Reduce initial doses if relative contraindications exist
- Use daily dosing if pain severity warrants it
- Prescribe a limited but long enough course if pain is acute and expected to be short lived

Examples of Initial Dosing Strategies and Considerations

- Petey: geriatric toy breed with CVHD
- Poppa: young dog with gunshot wound
- Abby: immediate post-amputation

Educating Pet Owners: Communication necessities

- Explain
  - Why you are prescribing an NSAID
  - What the known risks are
  - That dogs may be more likely to develop GI toxicity than people, especially if different NSAIDs are combined
  - Why you believe the benefits outweigh the risks in their dog
Educating Pet Owners: Communication necessities

**Ask**
- What other medications are you giving your dog?
- Are you using any topical, otic or ophthalmic preparations on your dog?
- Have you given an aspirin or other over-the-counter medications for pain?
- If so, when was the last dose given?
- Has your dog tolerated NSAIDs in the past?

**Provide**
- A copy of this information in writing
- Any written materials the manufacturer has included for the pet owner in the packaging

**Put on every NSAID prescription label:**
- Dosette or use and contact doctor if any loss of appetite, vomiting or change in stools is seen
Potential targets for adverse effects of NSAIDs

Gastrointestinal tract
Kidney tissue
Liver
Coagulation
Articular cartilage
Bone healing
Adverse drug-drug interactions

Relative frequency of reported adverse effects for all NSAIDs

- 64% Gastrointestinal
- 21% Renal
- 14% Hepatic
- NSAIDs approved for dogs are significantly safer than non-approved NSAIDs

Adapted from Lascalles 2012

GI Adverse Effects: Ulcer or not? How do you tell?

- Gastrointestinal effects (vomiting, diarrhea, anorexia) can occur INDEPENDENTLY of GI ulceration
- Vomiting is the most common sign of GI ulceration in the dog, but ulceration can occur with NO clinical signs
- GI adverse effects can occur at any time during the course of NSAID use
- Aspirin and maybe other NSAIDs can trigger GI “adaptation”
- Safest course of action is to instruct clients to discontinue use and contact a veterinarian if any change in GI function is seen during use
Renal Adverse Effects
- Prostaglandin E2 is important in the maintenance of renal perfusion during hypovolemia
- No adverse effects are expected with long term use in patients with normal blood pressure, volume status and sodium levels
- High doses of NSAIDs, Na depletion, hypotension, hypovolemia and anesthesia increase the risk of adverse renal effects
- Appropriate anesthetic management poses a low risk for renal toxicity
- Use NSAIDs cautiously in dogs with pre-existing kidney disease

Hepatic Adverse Effects
- NSAIDs are primarily excreted via hepatic metabolism
- Liver enzyme (ALT/AST/ALP) levels do not directly represent liver function levels
- Hepatic toxicity can occur with any NSAID
- Most NSAID associated hepatopathies occur within the first three weeks of therapy
- Dogs with hepatic dysfunction are at risk for GI ulceration; NSAIDs increase this risk
- Dose reduction is prudent for dogs with pre-existing hepatic dysfunction

Inducible vs. Idiosyncratic Hepatic Toxicity

<table>
<thead>
<tr>
<th>Inducible hepatotoxicity</th>
<th>Idiosyncratic hepatotoxicity</th>
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</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>Unpredictable, aberrant immunological response</td>
</tr>
<tr>
<td>Dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td>Predictable</td>
<td>No known risk factors</td>
</tr>
<tr>
<td>Causes rise in liver enzymes: ALT AST</td>
<td>Usually occurs within 90 days of starting therapy</td>
</tr>
<tr>
<td>Usually causes subclinical rise in LE</td>
<td>Causes elevations in all LE and total bilirubin</td>
</tr>
<tr>
<td></td>
<td>If diagnosed when subclinical, is reversible</td>
</tr>
<tr>
<td></td>
<td>If diagnosed with clinical illness, can be fatal</td>
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</tbody>
</table>
**Hints for interpreting liver enzyme elevations**

- Don’t get caught trying to determine NSAIDs role in LE elevations without having a pre-treatment liver profile.
- Alkaline phosphatase elevations are common in older dogs and usually related to non-pathological nodular hyperplasia.
- If AST/ALT elevations are due to drug reactions, they will reverse within a few weeks of discontinuing the drug.
- Use liver function indicators to decide whether NSAIDs are contraindicated.

**Drug Monitoring Plans**

- Prior to starting potentially long term NSAID use, baseline screening of CBC, chemistry profile and U/A are recommended.
- Recheck exam and at least a chemistry panel and a HCT/T7 after 3-4 weeks of NSAID therapy.
  - Adjust therapy based on results.
- Consider repeating screening in another 2 months for high risk patients.
- Full screening (same as baseline) should be done at least twice yearly for patients on chronic therapy.
- Recheck lab work on any sick patient receiving NSAIDs.

**Easy steps to prevent common adverse effects**

- Do not use NSAIDs in dogs with pre-existing GI disease or known compromise (like surgery).
- Consider label and published doses/dose intervals as MAXIMUM doses.
- Remind clients at every contact with your hospital to discontinue and notify you if their dog has signs of illness when NSAIDs are being given.
- Require blood and urine monitoring at least twice a year for patients on long term NSAIDs.
- Instruct owners to only give NSAIDs with food in the stomach or when eating.
Transitions between NSAIDs or between corticosteroids and NSAIDs

- Dogs have significant individual variation in response and side effects to different NSAIDs
- Changing to another NSAID may reduce side effects or improve efficacy
- Little data exists to guide the use of wash out periods
  - Plasma half-lives are known, but not tissue half-lives
  - Clinical efficacy can persist past expected interval predicted solely by plasma half-life
- Wait at least 7 days after aspirin therapy to start other NSAID treatment

Transitions between NSAIDs or between corticosteroids and NSAIDs

- If the transition is indicated because of adverse effects, wait until the patient is clinically normal
- If GI side effects are prompting the change, wait until GI function has been normal for several days
  - Consider the use of gastroprotectants like sucralfate or omeprazole
- If transitioning due to lack of efficacy, 5-7 days is a conservative recommendation; shorter times may be tolerated
-Prescribe rescue analgesics during the wash out period

Clinical signs that should prompt an exam and lab work

- Vomiting
- Change in stool color
- Diarrhea
- Anorexia
- Significant lethargy
- Pale mucous membranes
- Icterus
- Discolored urine
Minimizing NSAID Toxicity

- Stick to FDA approved NSAIDs with good safety profile
- Educate your clients verbally and in writing
- Don’t combine different NSAIDs or combine with any form of corticosteroids
- Remember that wash-out periods are defined for plasma only

Safe Use of NSAIDs in Dogs

- Dose to effect
- Pre-treatment monitoring and regular monitoring will catch most toxicity early
- Do lab work on any sick patients taking NSAIDs
- Only provide enough medication to cover the interval until the next scheduled monitoring

Don’t be afraid to use NSAIDs in old ladies like me. We need pain relief too!
Questions to the Speaker

Please email your questions to webconference@aahanet.org by Sunday, October 7, 2012.

Dr. Moses will provide written responses to all of the questions and they will be posted on AAHA’s website by Friday, October 19, 2012.

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Thank you for your participation!

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