Nonsteroidal Anti-inflammatory Drugs: A Tool for Managing Pain

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Classification of Pain

Pain Aδ + C Sensory Nerves

Physiological
- Nociceptive
- Protective

Inflammatory
- Tissue Trauma
- Resolves

Chronic
- Maladaptive
- Spontaneous/
Refractory

Neuropathic
- Maladaptive
- Nerve trauma

THE CLASSICAL “PAIN PATHWAY”

1. **TRANSDUCTION**
   - A sufficiently intense physical pain stimulus causes initiation of an action potential by either Aδ or C nociceptors.
     - A non-electrical stimulus is transduced into an electrical potential.

2. **TRANSMISSION**
   - The signal is transmitted along the peripheral sensory nerve to the dorsal horn of spinal cord.

3. **MODULATION**
   - The peripheral sensory nerve synapses with neurons in the dorsal horn.
   - The pain signal is modulated by interneurons and is either enhanced or diminished.

4. **PERCEPTION**
   - The peripheral sensory nerve synapses with second-order neurons of specific ascending spinal tracts within the dorsal horn.
   - The pain signal is projected to different areas within the brain where it is perceived as pain.
Inflammatory Pain Lowers Threshold of Nociceptors: Peripheral Sensitization

1) Julius D. Nature. 2001
Central Sensitization: Modulation and Modification of the Dorsal Horn Neurons

1) COX-2 enzymes are up-regulated at the surgical → prostaglandin (PG) synthesis
2) Increased COX-2 derived PGs correlated with increase post-op pain

1) COX-1 and COX-2 enzymes are constitutively expressed in dorsal root ganglia and spinal cord.
2) COX-2 enzymes up-regulation during pain
3) Circulating TNF-α and IL-1β can also up-regulate COX-2

Rimadyl Reduces Development of Peripheral And Central Sensitization
General Anesthetic Drugs Do Not

1) Malmgren AB. Science. 1992
2) Buvanendran A. Anesthesiology. 2006
3) Svensson CI. Ann Rev Pharmacol Toxicol. 2002
4) Samad TA. Nature. 2001
5) Beiche F. Inflamm Res. 1998
Preemptive analgesia: pain medication administered prior to painful injury
- Treat post-op pain by preventing establishment of central sensitization\(^1\)

Preventive analgesia: includes any analgesic that is administered during the entire perioperative period
- Goal: prevent peripheral and central sensitization.
- Include:
  - Initiating analgesia early
  - Ensuring degree of analgesia = degree of pain
  - Continuing analgesia until pain has subsided \(^2\)

- Research confirms preventive analgesia as the preferred approach for acute post-operative analgesia and to prevent chronic post-operative pain. \(^3\)

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Current FDA approved NSAIDS For Dogs and Cats

- Rimadyl®
- Metacam®
- Derramaxx®
- Previcox®
- Onsior®
- Galliprant®

- Metacam®
- Onsior®
## FDA Claims for Canine and Feline NSAIDs

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Postoperative Pain</th>
<th>Treatment of OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimadyl®</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Metacam®</td>
<td>✗ (cat)</td>
<td>✗ (dog)</td>
</tr>
<tr>
<td>Derramaxx®</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Previcox®</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Onsior®</td>
<td></td>
<td>✗</td>
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<tr>
<td>Galliprant®</td>
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<td>✗</td>
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</table>
Surgical analgesia due to early Inhibition of inflammation

Pre-incisional analgesia can interfere with development of peripheral and central sensitization

Vasodilation increases volume of distribution and tissue exposure to Rimadyl, and therefore increases tissue concentration.\(^1\)

High protein binding (>99) limits passage from plasma to tissues with the exception of inflammatory exudates.\(^2,3\)

inflammation increases protein concentration at the surgical site; Rimadyl shifts from plasma to Inflamed tissues

COINCIDES WITH UPREGULATION OF COX-2 ENZYMES\(^4\)

# Chronic verses Acute Pain Summary

<table>
<thead>
<tr>
<th>Acute Pain</th>
<th>Chronic Pain</th>
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</thead>
<tbody>
<tr>
<td><strong>Peripheral &amp; Central Hypersensitization</strong></td>
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</tr>
<tr>
<td><strong>Modulation of Pain Pathway</strong></td>
<td><strong>Modification of Pain Pathway – Prostaglandins One of the Mediators</strong></td>
</tr>
<tr>
<td><strong>Changes Are Temporary, Pain Resolve When Injury/Inflammation Resolves</strong></td>
<td><strong>Changes Are Long Lasting, Pain Does Not Resolve When Injury/Inflammation Resolves</strong></td>
</tr>
<tr>
<td><strong>Pain is Associated with a Defined Stimulus</strong></td>
<td><strong>Pain Can Be Spontaneous, Intermittent, Difficult to Control</strong></td>
</tr>
</tbody>
</table>
Do the Benefits of Using an NSAID Outweigh the Risks?

- There are risks and benefits with all commonly prescribed veterinary drugs, including NSAIDs
- All NSAIDs approved for oral use in dogs have been determined to be safe at the approved dose for the general population of dogs
- Adverse Events (reactions) or AEs (for all drugs) are divided into two groups:
  - Inducible
  - Idiosyncratic
## The Two Types of Drug Adverse Reactions

<table>
<thead>
<tr>
<th>Inducible</th>
<th>Idiosyncratic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactions are dose-related</td>
<td>Not dose-related</td>
</tr>
<tr>
<td>Reactions are attributable to the mechanism of action of the drug</td>
<td>Not attributable to the mechanism of action of the drug</td>
</tr>
<tr>
<td>Predictable</td>
<td>Unpredictable and rare</td>
</tr>
</tbody>
</table>
NSAID Mechanism of Action: Inhibition of Cyclooxygenase (COX) Enzymes

Arachidonic Acid

COX-1
Constitutive

Prostaglandins
Thromboxane

Hemostasis¹

Gastric mucosa protection²

Renal sodium and water absorption²

Inflammation, Pain, Fever

COX-2
Inducible

Prostaglandins
PGE2
PGI2

Renal blood flow in hypotensive state⁴-⁶

Gastric protection when GI tract inflamed⁷

The Risk of an Adverse Reaction is Greatest Early in Treatment (not with long-term use)

- The most common AEs seen with NSAIDs are inducible, and include GI irritation\(^\text{19}\)
- Idiosyncratic reactions occur infrequently (1 in 10,000)\(^\text{17,20}\)
- Idiosyncratic reactions are most likely to occur in the first 90 days of treatment\(^\text{14,27}\)
Clinical Considerations When Prescribing an NSAID

- Get a thorough history of previous medications and medical conditions
- Perform a thorough physical exam
- Screen patient for any underlying conditions
- Inform owner of potential risks and benefits
- Distribute Client Information Sheets
- Monitor and assess appropriately
Misconceptions About NSAID Adverse Events

- Some DVMs perceive that the risks outweigh the benefits
- Many myths exist around NSAID adverse events
- By better understanding adverse events:
  - Veterinarians are able to minimize their occurrence
  - Better communicate the actual risks to pet owner
Benefits/Risk of Treating with an NSAID Should Be Evaluated on a Patient by Patient Basis

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tbody>
<tr>
<td>Pain Relief</td>
<td>GI Signs</td>
</tr>
<tr>
<td>Relief of Inflammation</td>
<td>Renal Disease</td>
</tr>
<tr>
<td>Return to Function</td>
<td>Hepatic Disease</td>
</tr>
<tr>
<td>Re-establish Human–Animal Bond</td>
<td>Other Less Commonly Reported Signs</td>
</tr>
</tbody>
</table>

- Frequency is low for most adverse events and resolve with discontinuation and/or supportive treatment
- With appropriate patient selection and monitoring can maximize the benefits and minimize the risks
What are the Risks?

- Most common adverse reaction is GI, ranging from dyspepsia to GI perforation
- Renal Disease
- Hepatic Disease
- Other
- Frequency is low for most
- Can be minimized by appropriate patient selection and monitoring (See Risk Benefit discussion)
NSAIDs Removes Autoregulation of Blood Flow in the Kidneys

Fig. 1. Distribution of COX-1 and COX-2 in the human kidney.

Fig. 2. Role of prostaglandins in the kidney.

- **Arachidonic acid**
  - **PGE$_2$**
    - $\downarrow$ Na$^+$ reabsorption at the thick ascending limb of the loop of Henle
  - $\uparrow$ Renin release causing $\uparrow$ aldosterone, increasing K$^+$ excretion
  - Vasodilation $\uparrow$ Renal blood flow and GFR in stressed states

- **PGI$_2$**
NSAID Reduces the Protective Mechanisms of the Gastric Mucosa

Gastrointestinal (GI) Tract

- Upper GI complications have also occurred in pts treated with COXIBs
  - Perforation
  - Ulcers
  - Bleedings
  - PUBs
NSAIDs and Liver

- The liver is uniquely susceptible to damage by drugs
- Genetic polymorphism in hepatic enzymes involved in drug metabolism
  - Breed differences
  - Individual variation
- Idiosyncratic hepatotoxicosis has been documented with the use of NSAIDs in the dog\textsuperscript{1,2}
  - Most occur within first 90 days
  - Most dogs recover with immediate discontinuation of the drug and appropriate support
- Educate pet owners; monitor appropriately

Elevated Liver Enzymes May or May Not Preclude the Use of NSAIDs

- Elevations of hepatic enzymes often reported in older dogs
- NSAIDs use in these patients depends upon cause of enzyme elevation
  - Benign conditions – Nodular hyperplasia, breed (Scottish Terrier)
  - Disease conditions – hepatic disease, endocrinopathies, drug induced (steroids, phenobarbital, etc.), pancreatitis, neoplasia, current drug therapy, infectious disease, etc.
- Certain breeds predisposed to liver disease

<table>
<thead>
<tr>
<th>Bedlington Terriers</th>
<th>Doberman Pinchers</th>
<th>Cocker Spaniels</th>
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<tbody>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Labrador Retrievers</td>
<td></td>
<td></td>
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<tr>
<td>Dalmatians</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>West Highland White &amp; Skye Terrier</td>
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</table>

# Tailor Work-up of Elevated Liver Enzymes to The Patient

<table>
<thead>
<tr>
<th>Review CBC, Panel, UA</th>
<th>Review Medical History and Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested Tests – Dependent Upon Signalment, History and Clinical Signs</strong></td>
<td></td>
</tr>
<tr>
<td>• Hepatic Function Test</td>
<td>• Thyroid Panel</td>
</tr>
<tr>
<td>• Leptospirosis titers</td>
<td>• Urine Cortisol/Creatinine</td>
</tr>
<tr>
<td>• Pancreatic Lipase Immunoassay</td>
<td>• Low Dose Dex/ACTH Stimulation</td>
</tr>
<tr>
<td>• Abdominal Ultrasound</td>
<td>• Liver Aspirate/Biopsy</td>
</tr>
</tbody>
</table>
If Only ALP is Elevated and the Dog is Asymptomatic

- Could be Benign Nodular Hyperplasia\(^1\)
  - Is fairly common in older dogs
  - ALP can be 2.5x to >10x normal
  - Ultrasound and Bile Acids to rule out other disease
  - Additional diagnostic as needed

- Consider NSAIDs if no other underlying disease detected

- Monitor to ensure no further elevation or other abnormalities (within 10–30 days, then periodically)
  - Any further increases in hepatic enzymes warrants further evaluations\(^2\)

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NSAIDs **NOT RECOMMENDED** if Patient Has:

- Pre-existing hyperbilirubinemia
- Elevated ALT, AST and GGT
  - If any of these are elevated alone or in combination, with or with our signs of hepatic disease
- Decreased albumin—Recommend workup for renal, GI or hepatic dysfunction
- Elevated ALP *with* clinical signs of liver or Cushing’s disease
The Labrador Retriever Breed is overrepresented because:
- Most popular breed
- Has a high incidence of OA

Recently identified: Copper Associated Chronic Hepatitis (CACH) in Labrador Retrievers\(^1,2\)
- Dog can be asymptomatic
- Females > males?; middle age to older dogs
- Diagnosis: Elevation of ALT and ALP with a greater relative increase in ALT; histopathology with copper analysis

Screening and monitoring NSAIDs use in Labs, since CACH may be asymptomatic

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Minimizing the Risk: Patient Selection\textsuperscript{1-6}

- All dogs should undergo a thorough history & physical examination before initiating NSAID therapy
- Appropriate hematological & serum baseline data is recommended prior to and periodically during administration
- Avoid in dogs with a history of renal disease
- NSAIDs are not recommended for dogs with bleeding disorder
- Dogs that have adverse reactions from other NSAIDs, may have adverse reactions with other NSAIDs
- Dogs at greatest risk
  - Dehydrated or on concomitant diuretic therapy
  - Dogs with renal failure, cardiovascular and/or hepatic dysfunction

Minimizing the Risk: Concurrent Medications\textsuperscript{1-6}

- Concomitant use of NSAIDs with other anti-inflammatory drugs such as corticosteroids and other NSAIDs should be avoided
  - Pet owners may not disclose that they are treating dogs with aspirin
    - 7\% veterinarians recommend aspirin to treat canine osteoarthritis\textsuperscript{7}
    - 28\% of pet owner indicated that they use aspirin to treat their dogs osteoarthritis\textsuperscript{7}

- Studies to determine the activity of NSAIDs when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted

- Drug compatibility should be monitored closely in patients requiring cardiac, anticonvulsant and behavioral medications

5. Rimadyl Package insert, NADA 141- 111, 2007 Pfizer Animal Health,
6. \texttt{http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm}, FDA Website.
Minimizing the Risk: Pet Owner Communication¹-⁶

- Always provide a Client Information Sheet with prescription
- Pet owners should be:
  - Informed regarding potential adverse events
  - Advised to discontinue NSAID therapy if side effects occur and contact their veterinarian
  - Store palatable formulations out of reach of dogs, in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested
  - Made aware of the importance of periodic follow-up for
    • Safety, Efficacy, Compliance
    • Development of unrelated conditions

5. Rimadyl Package insert, NADA 141-111, 2007 Pfizer Animal Health,
The Best Course of Action is to Focus on *Early* Diagnosis and *Consistent* Treatment!

- DVMs frequently limit NSAID use to moderate or late stage OA
- Some veterinarians use as last resort
- Intervention prior to the onset of pain in osteoarthritis is challenging

**Effective Treatment with NSAIDS**
- Reduces inflammation – slows or eliminates further progression
- Prevents wind-up
Consequences of Waiting

“The changes associated with osteoarthritis ultimately have an impact on the patient through decrease ability to use the joint or the production of pain or both. Unfortunately once these changes are severe enough to be recognized clinically, they are likely to be irreversible with current treatments.”

Because windup is more difficult to treat, one treatment modality may not control the multiple receptors that have been activated in chronic pain

Most Information for Treatment of Canine OA is on NSAIDS

- NSAIDs:
  
  - Improved activity and showed progressive improvement in clinical signs of OA with long term treatment\textsuperscript{1,2,3}
  
  - NSAIDs break the progressive cycle of inflammation and pain by acting in both the joint and the dorsal horn.\textsuperscript{4}
  
  - For most dogs, the benefits of using NSAIDs outweigh the risks.\textsuperscript{2,3}

More than “Just Pain Medicine”

The primary pharmaceutical therapy used for pain management of OA in dogs is NSAIDs

- Anti-inflammatory effects of NSAID may provide disease altering benefits in OA patients, improve recovery from surgery 1-3
  - NSAID therapy provides analgesic benefits that allows appropriate exercise
  - Rehabilitation therapy & appropriate exercise enhance joint function, mobility, and maintenance of muscle tone
  - NSAIDs have been shown to effectively control the pain and inflammation associated with osteoarthritis and as a result activity4,5

Key Point to Consider When Choosing an NSAID

- Overall, all NSAIDs are equally efficacious for osteoarthritis and have similar safety profiles

- Choice is dependent on the individual patient
  - One drug maybe more effective than another drug
  - One drug may be better tolerated
  - Pharmacogenetics?

- Start treatment using preferred NSAID
  - Pre-treatment blood work

- Monitor – efficacy and safety

- If need to switch – 3-5 days based on PK (not clinical studies)
References


