Canine OA Management: Maximizing Benefits, Minimizing Risks

By Duncan Lascelles, BVSc, PhD, DACVS, MRCVS

AAHA gratefully acknowledges Pfizer for their sponsorship of this webcast.

Seminar Outline

• What is OA, and how does it manifest clinically?
• Multidimensional management challenges
• Treatment approach and multimodal treatment
• NSAIDs: maximizing benefit
• NSAIDs: minimizing risks
An Underestimated Disease?

- 20% of canine population have clinical OA (Johnston et al, VCOT, 1994)
  - Higher % in older dogs
  - Most common chronic pain in practice population
- Very common reason for euthanasia
  - Leading cause in MWDs (Moore et al 2001)
- Owners very often dissatisfied and frustrated by attempts to manage chronic OA
- Progressive, incurable disease with multidimensional effects

How Does the Disease Manifest Clinically?

≠
Multidimensionality of OA

• OA is not just joint pain
• Multidimensional disease:
  • Joint pain
  • Mobility impairment
  • Activity impairment
  • Behavioral changes
  • Affective impact
  • Musculoskeletal changes
    • Local and distant effects
    • Muscle mass and tone
    • Ligament and tendon health

Challenges of Managing OA

• Primary Pathology
  • Cartilage destruction

• Extended Pathology
  • Chronic (undulating) synovitis
  • Degradation of other joint structures
  • Adjacent muscle weakening and loss
  • Nervous system sensitization
  • Chronic widespread musculoskeletal changes
  • Behavioral changes
## Treatment of Canine OA

Treatment should be:
- Targeted and individualized
  - Comprehensive assessment and reassessment critical
- Appropriately multimodal
  - Address peripheral and central sensitization
  - Address the multiple dimensions of adverse changes
- Initiated early & focused on prevention
- Lifelong
  - Need a logical approach to this with focus on lifestyle changes

## Medical Options

- **‘Base’ analgesics** (NSAIDs; Acetaminophen; Steroids)
- Weight management
- Diet modulation (type; amount; supplements)
- Exercise; physical rehabilitation; physical modalities
- Adjunctive analgesics (tramadol, amantadine, gabapentin, TCAs, PSGAGs)
- Acupuncture
- Chemical desensitization (local)
- Neuroablative procedures (central)

## What Works?
Evidence From Studies in Humans

OARSI recommendations for the management of hip and knee osteoarthritis
Part III: changes in evidence following systematic cumulative update of research published through January 2009

Treatment Efficacy

- NSAIDs
- Weight Management / Dietary Modulation
- Exercise
AAHA Webcast: Canine OA Management: Maximizing Benefits, Minimizing Risks

NSAID Use

## NSAIDs

- Drug Differences
- Efficacy
- Toxicity
- Duration of use
- Dose reduction
- Timing of treatment
- Patient screening
- Owner education
- Dose
- Concurrent drugs

### NSAID Use

- **Patient screening**
- **Owner education**
- **Dose**
- **Concurrent drugs**

### Duration of Use

1. 2-3d
2. 7d
3. 14d
4. 28d
5. Over 28d

### Long-term Use of NSAIDs and Efficacy

- Evidence that long term use (>30 days) of the approved dose leads to increased efficacy

**Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis**

J. F. Innes, J. Clayton, R. D. X. Lazellles

*Veterinary Record, 2010*

- 4 months of daily carprofen (4mg/kg)
- 110 chronic OA dogs: 70% hind limb

Why the Improvement Over Time With NSAIDs?

- Decrease in inflammation
- Greater ability to exercise
  - Producing pain relief (endogenous analgesic systems)
  - Greater muscle mass and joint control / stability
- Decrease in Central Sensitization
  - Direct effect of NSAIDs
  - Indirect effect of endogenous analgesic systems

Fear of Using NSAIDs For Extended Periods

- 8 year old Labrador
- THR 3 years ago
- On tramadol, nutritional supplement, OA diet
- BCS = 4
- Significant problems on the left hind
Long-term Use of NSAIDs and Side Effects

- No evidence that long-term NSAID use (at a standard approved dose) increases incidence of side effects
    - No correlation between adverse event rates and length of treatment ($r_s = -0.109; P=793$)
  - Most side effects occur within 2 – 4 weeks
  - Use of higher than approved doses increases incidence of side effects

Timing of NSAID Use

- Predictable pain relief prevents deterioration of the musculoskeletal system

Putter

- 14 month old English Setter; 19kgs
- Limited exercise; overweight; significant hip pain

- Initiate:
  - NSAID (caprofen, 25mg BID)
  - Fish oil supplement
  - Increasing exercise
  - Weight loss plan
Putter

- End result:
  - Increased and maintained exercise
  - Weight loss – steady at 16 kgs; BCS = 5
  - Maintained fish oil supplementation; added in G-CS
  - 9 months of carprofen (25mg BID for 4 months then reduce dose to 25mg SID)
  - Maintained good muscle mass; good ROM

Dose Reduction and Efficacy

- Wernham et al (in press) Dose reduction of meloxicam in dogs with OA-associated pain and impaired mobility. JVIM

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Maintained Dose</th>
<th>Reduced Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14 - 27</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>28 - 41</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>42 - 55</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>56 - 69</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>70 - 83</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>84 - 97</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>98 - 112</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Dogs left study if owners considered pain control insufficient
Dose Reduction and Efficacy

- Dose reduction can be successfully employed
- Best way to perform dose reduction is not known
- Appears to be individual dog dependent
  - Requires follow up assessments
  - Success due to:
    - Increased exercise and muscle mass
    - Reversal of Central Sensitization
- Human study (Luyten et al 2007, Ann Rheumat Dis)
  - 24 week study
  - Continuous vs. Intermittent celecoxib
  - Significantly fewer (P=0.031) flare-ups in the continuous group

Nociceptive Pain

OA Pain
Peripheral and Central Sensitization

• Amplification and facilitation of nociceptive signals
• Innocuous signals interpreted as painful
• Poor initial response to analgesia
• Negative effect on muscles and joints
• Cannot measure or predict which animals have these changes
• Complex changes; lots of failsafe in the system to ensure pain is perceived

Neurobiological Mechanisms of Chronic DJD-Associated Pain

• Changes in Na+ and K+ channels
• NMDA mediated cellular wind-up and central hyperexcitability
• Upregulation of COX (2) and prostanoids
• Ca²⁺ channel activity increase (alpha-2-delta subunits)
• Glial cell activation and facilitation
• Increased sympathetic activity
• Changes (down-regulation) in opioid, nor-adrenaline (NA) and serotonin (5-HT) systems

Multimodal Drug Therapy

• Useful to help control pain when NSAIDs not fully effective
• Theoretically a good idea; little hard evidence of analgesic effects
  • Evidence:
    • Amantadine: single study; positive; 31 dogs (placebo & treatment)
    • Gabapentin: -
    • Tramadol: -
    • PSGAGs: single study; not significant; 84 dogs (placebo & 3 different doses of treatment)
Multimodal Drug Therapy: Tramadol

- No studies evaluating or reporting efficacy
- Several studies evaluating pharmacokinetics
  - Very poor oral or rectal absorption
  - Little production of active M1 metabolite
  - Little evidence of favorable PK data
  - PK very different compared to humans
- No studies evaluating safety or side effects
- Basic science cautions against combination with NSAIDs
  - Some dose combinations antagonistic
  - Potential for worse gastro-intestinal lesions

Multimodal Drug Therapy in OA

- Adjunctive part of treatment – not to be relied upon
  - Not a replacement for NSAIDs
  - Not a replacement for non-drug therapies
  - Very little known about effectiveness and side effects
  - Most evidence of efficacy in dogs that are not fully responsive to NSAIDs

NSAID-Related Toxicity

- All the NSAIDs can be associated with toxicity
  - GI 64%
  - Renal 21%
  - Hepatic 14%

- Total level of NSAID-related toxicity is likely the same for all approved NSAIDs
- Approved NSAIDs are significantly safer than non-approved (Reimer et al 1999, JVIM; Sennello et al 2006, JVIM)

- Risk is minimized by 'Appropriate use'
Minimizing Toxicity

- Selection of patients
  - Risk factors for GI, renal and hepatic side effects
- Owner education
  - Discuss signs of toxicity
  - Dispense owner information sheets
- Dose selection
  - Initial selection
  - Monitoring
- Concurrent drug use
  - Monitor medical record
  - Question owner

Selection of Patients

- Liver toxicity and liver dysfunction associated risks

Idiosyncratic Hepatotoxicity

- In humans, most often associated with diclofenac and sulindac
- Apparent incidence rate of severe 1 to 2 cases per million prescriptions (Purcell et al 1991) to 6 to 18 cases/100,000 person-years (Walker 1997)
- Theory: generation of reactive acyl glucuronide metabolites, promoting an immunological response (Boelsterli 2003)
Liver

- Idiosyncratic reactions occur in dogs: documented for carprofen
- Hepatotoxicity seen with all approved NSAIDs
- Incidence - unknown
  - Considered extremely low
- Risk factors for NSAID-induced hepatotoxicity
  - Unknown
  - Raised liver enzymes are not a risk factor

Liver Enzymes

- Liver enzymes often raised in OA dogs
- Raised liver enzymes not of concern (with respect to NSAIDs)
- Decreased liver function is a concern
  - Increased risk of GI ulceration associated with liver dysfunction
  - Decreased drug metabolism
- Evaluation of liver function
  - Serum bile acids
  - Urinary bile acids

Liver Enzymes and NSAIDs

Use NSAIDs for OA
- Appropriate monitoring

↑Liver enzymes
- ↑mild; historically stable
- ↑moderate; historically rising

Chemistry

Evaluate liver
- (exam; US; Bx)

Serum Bile Acids

Normal

Monitor & Evaluate liver

Elevated

Do NOT use NSAIDs
- Evaluate liver
  - (exam; US; Bx)
Claire
- R tarsal and L stifle OA - pain and impairment
- Considering NSAID treatment
- Hematology: normal
- Chemistry:
  - AlkP 155 U/l (14-120)
  - ALT 154 U/l (16-73)

Charlie
- 31kg, 7 year old Labrador
- Bilateral hip OA - pain and decreased function
- NSAIDs part of the treatment plan
- CBC: normal
- Blood biochemistry:
  - Alkaline phosphatase 270 (normal range 12-150iu/l)
  - ALT 188 (normal range 5-105iu/l)
  - (albumin normal)
- Bile acids: elevated

Concurrent Drug Use
Concurrent Drug Administration

- In a large proportion of ADE cases, there was concurrent administration of another NSAID, or a steroid.

- Systemically administered steroids result in additive GI side effects when administered with an NSAID in dogs:
  - Dow et al (1990) AJVR 51:1131-8

Concurrent Drug Administration

- Careful review of record
- Careful history from owner
  - 30% of dog owners may use aspirin

- Sources of steroids
  - Endogenous
  - Exogenous
    - Prednisone / Prednisolone
    - Depo-preparations (subcutaneous; intra-articular)
    - Topical steroid-containing preparations (creams, sprays, ointments)

Topical Steroids

- Steroids present in a large proportion of commercial otic and skin products (creams, sprays, ointments)
  - DVMax (betamethasone)
  - Tresaderm (dexamethasone)
  - Panolog (triamcinolone)
  - Mometamax (mometasone)

- No information on safety of topical steroids with concurrent NSAIDs
- Systemic absorption appears to increase with increasing potency.
Topical Steroids

- Suppression of the adrenocortical axis in 0%, 9%, 17% and 50% of dogs treated with Mometamax, DVMax, Panalog and Tresaderm respectively after 7 days of treatment.

Seminar Outline

- What is OA, and how does it manifest clinically?
- Multidimensional management challenges
- Treatment approach and multimodal treatment
- NSAIDs: maximizing benefit
- NSAIDs: minimizing risks

Questions?
Questions to the Speakers

Please email your questions to webconference@aahanet.org by Sunday, November 6, 2011.

Dr. Lascelles will provide written responses to all of the questions and they will be posted on AAHA’s website by Friday, November 18, 2011.

Instructions for CE Certificate

1. To complete the evaluation, please go to the following website:
   http://www.keysurvey.com/survey/388484/1067/

2. After completing the evaluation, you will automatically be linked to the Continuing Education Certificate. The CE certificate can only be accessed after the evaluation is completed.

3. Download the CE Certificate (in PDF format) to your computer and print enough copies for those persons viewing the web conference with you.

Thank you for your participation!