Inflammatory pain in cattle

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Inflammation – an everyday occurrence
Inflammation – an everyday occurrence
Inflammation – an everyday occurrence

Pathophysiology of inflammation and pain
Rubor et tumor cum calore et dolor

Aulus Cornelius Celsus (c. 25 BC – c. 50 AD)

Pain is a cardinal part of inflammation
Inflammation

Membrane Phospholipid

Cyclo-oxygenase

PGH2

PGI2

PGD2

PGE2

(Prostacyclin)

PGF2

Lipoxygenase

Hydroperoxyeicosatetraenoic

Anandamide

Leukotriene A2

Leukotriene B2

Leukotriene D4

Leukotriene E2

Inflammation is a complex and intricate process

Neurogenic Inflammation

Tissue injury or infection

Neuropeptides

Calcium

Endothelial cells

Inflammatory mediators

NF-kB

Beads and PECs

IL-1, TNF

RSK, RIP1

G-protein

MAPK

ERK

JNK

p38 MAPK

P38

Lymphocytes

Peripheral sensitization

Peripheral nerve terminal of nociceptor neurons
Important concepts in pain physiology

Gottschalk et al., Am. Fam. Phys. 2001

Allodynia

STINE JACOBSEN LECTURE NOTES
If left untreated, inflammatory pain becomes chronic.
Effective treatment of inflammatory pain

Ineffective treatment of inflammatory pain
Acute inflammatory pain is easy to treat

Diagram:

- Membrane Phospholipid
  - Phospholipases
    - Arachidonic Acid
  - Cyclooxygenase
    - PGG2
    - PGH2
  - PGD2
  - PGE2
  - PGJ2 (Prostacyclin)
  - PGF2
  - Thromboxane
  - Vasodilatation
  - Vasoconstriction
  - Platelet aggregation
  - Increased vascular permeability
  - Bronchoconstriction

- Leukotriene A2
- Leukotriene B2
- Leukotriene C2
- Leukotriene D2
- Leukotriene E2
- Leukotriene E2 (Resolvase)
Obstacles for treatment of inflammatory pain

Reasons for not using analgetics

- Financial reasons: only 25-45% of farmers are willing to pay for analgetics (studies from USA, Canada, Italy)
- Farmers cannot diagnose pain
- Farmers have inadequate knowledge of available analgetics
- It is generally not cost-effective to provide analgesia (limited effect on production outcomes such as average daily gain, feed intake, or feed to gain)
Diagnosing pain

• Physical
  • Increased heart and respiratory rate
  • Increased rectal temperature
  • Reduced appetite and weight loss
  • Reduced milk production
• Behavioural

Subtle differences in resting behaviour after castration

Musk et al., Animals 2017
Cesarean section

Diagnosing pain – changes in behaviour

Table 1
Description of behaviour changes and score evaluation scheme.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description of Behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Always observe the attentive towards the surroundings? Is the cow active, preferring normal cow activities such as eating, rumination or licking? Is the cow facing the wall? Gunning film (comparative) or is the cow released and following activities in the near surroundings? The cow's should be evaluated when the cow is unattended.</td>
</tr>
<tr>
<td>Head bent</td>
<td>The head bending is considered before the cow, behind the cow, at a level or above the level. The total position may be evaluated when the cow is standing, walking or lying down. (not sleeping)</td>
</tr>
<tr>
<td>Eye white</td>
<td>The properties of white visible in the eyes of the cow.</td>
</tr>
<tr>
<td>Rectif. dist.</td>
<td>Evaluation of the presence of udder discharge and of whether the action of cleaning the udder has been observed. Deit or seed on the udder is not considered a lack of rectif. cleanliness</td>
</tr>
<tr>
<td>Sweating</td>
<td>Sweating without feed in the mouth</td>
</tr>
<tr>
<td>Head dropping</td>
<td>Pivoting the head downward, resulting in a croaking sound</td>
</tr>
<tr>
<td>Head raising</td>
<td>Meaning or grinning, usually on expiration</td>
</tr>
<tr>
<td>Muscle tense</td>
<td>Abdominal sweating with little production of either faces or urine</td>
</tr>
<tr>
<td>Interposition</td>
<td>Erect hair on the neck and back</td>
</tr>
<tr>
<td>Response to approach</td>
<td>The response of the cow clearly when approaching the cow directly to the level of the observer's waist, reaching towards the cow</td>
</tr>
<tr>
<td>Back position</td>
<td>The contour of the top line of the standing or walking cow</td>
</tr>
<tr>
<td>Weight shifting</td>
<td>Frequent unprovoked stepping and kicking with the hind limbs</td>
</tr>
</tbody>
</table>

Gleerup et al., Appl. Anim. Behav. Sci. 2015
Diagnosing pain – the pain face

(bii) (bii)

(biii)
Obstacles for appropriate treatment of pain

**Reasons for not using analgetics**


- Financial reasons: only 25-45% of farmers are willing to pay for analgetics (studies from USA, Canada, Italy)
- Farmers cannot diagnose pain
- Farmers have inadequate knowledge of available analgetics
- It is generally not cost-effective to provide analgesia (limited effect on production outcomes such as average daily gain, feed intake, or feed to gain)

Inadequate knowledge about available analgetics

**Literature search for species + NSAID**

- Dog & cat: 500 publications
- Horse: 200 publications
- Cattle: 100 publications
- Swine: 50 publications
Very few studies compare efficacy of different NSAIDs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lung consolidation (median %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftiofur</td>
<td>15.3</td>
</tr>
<tr>
<td>Ceftiofur + carprofen</td>
<td>5.5</td>
</tr>
<tr>
<td>Ceftiofur + ketoprofen</td>
<td>6.3</td>
</tr>
<tr>
<td>Ceftiofur + flunixin</td>
<td>1.7*</td>
</tr>
</tbody>
</table>

Lockwood et al., Vet. Rec. 2003

Obstacles for appropriate treatment of pain

Reasons for not using analgetics

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Use of analgetics is not cost-effective

Musk et al., Animals 2017

Use of analgetics is not cost-effective

### Mastitis

#### Table

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sulfa-TMP 1</th>
<th>Sulfa-TMP + Ketoprofen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>166 (81.0%)</td>
<td>54 (94.7%)</td>
</tr>
<tr>
<td>Blind quarter</td>
<td>15 (7.3%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Culled</td>
<td>24 (11.7%)</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>205 (100%)</td>
<td>57 (100%)</td>
</tr>
</tbody>
</table>


#### Graph

McDougall, J. Dairy Sci. 2009
Table 1
Examples of published surveys of public attitudes regarding the importance of pain in farm animals

<table>
<thead>
<tr>
<th>Statement</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>“It is wrong to cause farm animals any pain, injury or stress”</td>
<td>64% agree</td>
</tr>
<tr>
<td>“Farm animals should be protected from feeling physical pain”</td>
<td>72% agreed</td>
</tr>
<tr>
<td>“It is of no concern to me whether farm animals feel emotional pain”</td>
<td>73% disagree</td>
</tr>
<tr>
<td>“Farm animals have roughly the same ability to feel pain and discomfort as humans”</td>
<td>61% agreed</td>
</tr>
</tbody>
</table>
NSAIDs registered for cattle

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Dose</th>
<th>Half-life</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunixin meglumin</td>
<td>2.2 mg/kg</td>
<td>3-8 hours</td>
<td>IV q 24 hours</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>3 mg/kg</td>
<td>30 minutes</td>
<td>IV (IM) q 12-24 hours</td>
</tr>
<tr>
<td>Carprofen</td>
<td>1.4 mg/kg</td>
<td>30 hours (longer for calves)</td>
<td>IV or SC</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.5 mg/kg</td>
<td>20-40 hours</td>
<td>IV or SC (PO) q 24-72 hours</td>
</tr>
</tbody>
</table>

Transdermal flunixin
Other analgetics

- Local analgetics
  - Procain
- Alpha2-agonists
  - Xylazin
  - Detomidin
- Ketamin
- Opioids
  - Butorphanol
Systemic administration

- Alfa2-agonists
  - Xylazin: 0.05-0.3 mg/kg
  - Detomidin: op til 0.08 mg/kg
- Opioids
  - Butorphanol: 0.05 mg/kg
  - Ketamin
    - Up to 1 mg/kg

- Drawbacks
  - Sedation
  - Short action
  - Repeated IM injections
  - Constant rate infusion
  - Can become expensive

Epidural administration

- Local analgetics
- Alfa2-agonists
- Ketamin
- Opioids?
Epidural analgesia w/ xylazine
- Master’s thesis by Sidsel Sten Andersen

Table 1. Scoring of analgesia, sedation and ataxia

<table>
<thead>
<tr>
<th>Analgesia</th>
<th>Sodation</th>
<th>Ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No analgesia</td>
<td>No sedation, bright and alert</td>
<td>Gentle push on hind quarters elicits normal righting response</td>
</tr>
<tr>
<td></td>
<td>Normal avoidance response as established prior to trial, kicking, leg lifting, tail twirling</td>
<td></td>
</tr>
<tr>
<td>Mild analgesia</td>
<td>Mild sedation, decreased response to the environment and decreased alertness</td>
<td></td>
</tr>
<tr>
<td>Moderate analgesia</td>
<td>Moderate sedation, lowering of the head, Paresis of eyelids, Lethargy</td>
<td></td>
</tr>
<tr>
<td>Complete analgesia</td>
<td>Heavy sedation, Marked lowering of the head, Paresis of eyelids, Complete ataxia, Recumbent</td>
<td></td>
</tr>
</tbody>
</table>

1. Mild analgesia
2. Moderate analgesia
3. Complete analgesia
Nerve blocks

Nerve blocks
Regional perfusion (Bier block)

Infiltration analgesia
Infiltrationsanalgesi

Take-home messages

• Inflammation causes pain
• Acute inflammatory pain is easy to treat
  • NSAIDs
• Chronic pain with sensitization/wind-up is more difficult to treat
  • Multimodal approach
• Analgetics can be administered in many ways
• Limited knowledge and limited availability of drugs impedes treatment of pain in cattle
  • Pain recognition tools