Pain management and chemical restraint in cattle

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Things that Reportedly Taste Like Chicken

- Crocodile
- Rat
- Escargot
- Snake
- Emu
- Crickets
- KFC

Chickeny-ness
What are the take-home messages from this presentation

- Oral aspirin has poor bioavailability in cattle
- Sodium salicylate in the water can provide effective analgesic/anti-inflammatory concentrations in calves
- IM Xylazine-Ketamine-butorphanol provides excellent chemical restraint but pain can alter the PK
- Oral meloxicam tablets have 100% bioavailability in calves and cost $0.25/100 lbs.
- Oral gabapentin may be effective against chronic pain
Animal Welfare Policies and the Livestock Industry
Will it be a carrot or a stick?

- Easy to implement into existing production systems
- Inexpensive
- Quantifiable production benefits
- Access to new markets

- Increase the cost of production
- Poorly understood and ill-conceived (Blindfolded- swinging at a pinata)
- Legislation and trade policy
- Participation in mandatory “Welfare Assurance Schemes” to access markets
Pain Management Challenges

- Acute vs. Chronic Pain
  → “Wind-up” AKA central sensitization
- Pre-emptive vs. post-emptive pain management
- Availability of pain management compounds
- Duration of activity of pain management compounds
What about NSAIDs?

- Both central and peripheral analgesic effects ⇒ How readily do analgesics used in vet med cross the BBB?
- May act synergistically with other analgesics in a multimodal analgesia
- COX-2 drug activity is primarily central
  → 2 – 4 hours for mRNA expression after a painful event)
### NSAIDs currently used in cattle in the U.S.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Species</th>
<th>Indications</th>
<th>Dose (Cattle)</th>
<th>$T\ 1/2$</th>
<th>Withhold period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunixin meglumine injection</td>
<td>Cattle, horses and pigs</td>
<td>NSAID-Antipyretic, Anti-inflammatory</td>
<td>2.2 mg/kg IV ONLY!</td>
<td>3-8 h</td>
<td>Meat- 4 days Milk- 36 hours</td>
</tr>
<tr>
<td>Phenylbutazone injection</td>
<td>Horses and dogs</td>
<td>NSAID-Anti-inflammatory</td>
<td>4 mg/kg IV ONLY!</td>
<td>40 – 55 h</td>
<td>Not approved in cattle</td>
</tr>
<tr>
<td>Ketoprofen injection</td>
<td>Horses and dogs</td>
<td>NSAID-Anti-inflammatory</td>
<td>1.5 mg/kg</td>
<td>0.42 h</td>
<td>Not approved in cattle</td>
</tr>
<tr>
<td>Aspirin bolus</td>
<td>No FDA approval Horses and Cattle</td>
<td>NSAID-Reduction of fever</td>
<td>50 – 100 mg/kg Oral F &lt; 20%</td>
<td>0.5 h (IV salicylate)</td>
<td>No formal FDA approval Not for use in lactating cattle</td>
</tr>
</tbody>
</table>
Non-steroidal Anti-inflammatory Drugs (NSAIDs)

- **Flunixin meglumine**
  - $T\frac{1}{2} - 3 - 8\text{ hours}$
  - This class has recognized analgesic effects although these have not been quantified in published literature
  - I have no idea how the dose of 2.2 mg/kg was derived

→ **IV ADMINISTRATION ONLY**
Phenylbutazone

- **EXTRALABEL USE IN FEMALE DAIRY CATTLE OLDER THAN 20 MONTHS PROHIBITED**
- **ZERO TOLERANCE IN MEAT & MILK AND EGGS**
- **Respiratory arrest in cattle pretreated with phenylbutazone and anesthetized with xylazine and ketamine**
This guy knows more than the FDA about the analgesic effects of aspirin in cattle

Aspirin?

With apologies to Dr. Apley
Salicylic Acid Derivatives

- First NSAIDs used in modern medicine
- Veterinary forms have never been formally approved by FDA-CVM
- Does not cause bleeding disorders in cattle
- Dose rate of 50 – 100 mg aspirin/kg used

Gingerich (1975) Pharmacokinetics and Dosage of Aspirin in Cattle. JAVMA, 167 (10), 945-8.
Plasma Cortisol (nmol/L) & Salicylate (mcg/ml) Concentration following IV Sodium Salicylate or Oral Aspirin administration at 50mg/kg prior to castration.
Oral Sodium Salicylate

<table>
<thead>
<tr>
<th>Plasma Salicylate (100 mg/kg SS PO)</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>41.34</td>
<td>2.01</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hours)</td>
<td>2.08</td>
<td>0.49</td>
</tr>
<tr>
<td>AUC (hr*mg/L)</td>
<td>360.40</td>
<td>12.67</td>
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<tr>
<td>$T\frac{1}{2}$ (hours)</td>
<td>4.31</td>
<td>0.42</td>
</tr>
<tr>
<td>Bioavailability (F) %</td>
<td>61.05</td>
<td>0.02</td>
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<tr>
<td>V/F (L/Kg)</td>
<td>1.83</td>
<td>0.165</td>
</tr>
<tr>
<td>$K_{01}^{\text{absorption}}$</td>
<td>1.78</td>
<td>0.379</td>
</tr>
<tr>
<td>$K_{10}^{\text{elimination}}$</td>
<td>0.14</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Can oral sodium salicylate be used to provide prolonged analgesia in cattle?

- Study to measure the effects of oral analgesia and IM sedative analgesia on pain and distress following dehorning and castration.
- Experiment provided oral salicylate in the drinking water at 5 – 15 mg salicylate/mL of drinking water.
- Water provided from 24 hours prior to sham dehorning and castration to 70 hours post dehorning and castration (6 days).
Multimodal Analgesia Attacks Different Points Along the Pain Pathway

- Opioids
- $\alpha_2$-Agonists
- Centrally acting analgesics
- Anti-inflammatory agents (COX-2 specific inhibitors, nonspecific NSAIDs)

Ascending Input

Spinothalamic Tract

Dorsal root Ganglion

Peripheral nerve

Peripheral Nociceptors

Descending Modulation

Dorsal Horn

Trauma

Source: Adapted from Gottschalk A et al. Am Fam Physician. 2001;63:1979-84

http://www.physweekly.com/picts/specialxxi03/chart-b.jpg
40 Calves  
2-4 months 108 - 235 kg

Group 1  
Control

Group 2  
Oral Sodium Salicylate

Group 3  
IM Xylazine, Ketamine, Butorphanol

Group 4  
Oral Sodium Salicylate & IM Xylazine, Ketamine, Butorphanol

Day -5  
Acclimation to individual housing facilities  
Calf Weights  
 Determination of Water Intake

Day -3  
Jugular Catheter Placement  
Water Weights/Calf Weights  
SAL treatment initiated in drinking water (Group 2 & 4)

Day -2 (Period 1)  
Restraint  
Baseline Blood Sample (T0)  
Calf Weight  
IM XKB Injection (Groups 3 & 4) immediately prior to sham Castration & Dehorning  
Chute Exit Speed  
Blood Sampling  
(5, 10, 20, 30, 40, 50, 60, 90 minutes and 2, 3, 4, 6, 8, 10, 12, 18, 24 hours)

Day 0 (Period 2)  
Restraint  
IM XKB Injection (Groups 3 & 4) immediately prior  
Baseline Blood Sample (T0)  
Calf Weight  
Castration & Dehorning  
Chute Exit Speed  
Blood Sampling  
(5, 10, 20, 30, 40, 50, 60, 90 minutes and 2, 3, 4, 6, 8, 10, 12, 18, 24 hours)

Day 1-3  
Behavior Scoring  
Cessation of Sodium Salicylate treatment (Day 3) for Groups 2 & 4  
Calf Weights

Pharmacokinetic Modeling of Plasma Salicylate and XKB  
Modeling of Serum Cortisol
Sedative-analgesic drug combination ("Ketamine Stun") with salicylate in the drinking water

- Alpha-2 agonist xylazine at 0.05 mg/kg IV
- Dissociative anesthetic ketamine at 0.1 mg/kg
- Opioid butorphanol can be added at 0.025 mg/kg for surgical cases
- IV, IM or SC
  - SC administration reduces risk of recumbency
  - 1/20th of anesthetic dose
- Onset 5 – 10 minutes → duration 60 – 90 min
- Supplement with 25 – 50% of original dose
Dose; Standing Stun

- **Butorphanol**
  - 0.025 - 0.01 mg/kg
  - 5 - 10 mg

- **Xylazine**
  - 0.02 - 0.05 mg/kg
  - 10 - 20 mg

- **Ketamine**
  - 0.04 - 0.1 mg/kg
  - 20 - 40 mg

@ 450kg animal

**Note:** 1 – 2 – 4 Ratio to butorphanol
Difference between standing stun and recumbent stun

- Xylazine (0.025-0.05 mg/kg) (same as standing stun),
- Butorphanol (0.05-0.1 mg/kg) (10 x standing stun), and
- Ketamine (0.3 - 0.5 mg/kg) (5X standing stun) is administered IV.

- Onset is 1 minute, lasts 15 – 25 minutes
- Patients gracefully become recumbent
Difference between Stun and anesthesia

- Xylazine (0.05 mg/kg IV) first followed by ketamine (2 mg/kg IV) (20x standing stun dose) once sedated.
  → 15 minutes of anesthesia

- Combination of xylazine (0.05–0.1 mg/kg IM) and ketamine (4 mg/kg IM)
  → 30–40 minutes of recumbency

  → ½ dose to increase duration by 20 min
BHX Anesthesia (a 10x protocol)

- Combination administered IM
  - Butorphanol (0.0375 mg/kg)
  - Xylazine (0.375 mg/kg)
  - Ketamine (3.75 mg/kg)
- Onset in 3 -5 minutes
- Duration of activity 20 – 30 minutes
- Longer lateral recumbency compared with other regimens
Considerations for general anesthesia

- Catheterize the animal
- Protect the airway
- Monitoring
- Eye protection

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Fasting Duration</th>
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<tbody>
<tr>
<td>400 lbs. (or 6 months of age)</td>
<td>12 hours</td>
</tr>
<tr>
<td>1500-1800 lbs.</td>
<td>18 hours</td>
</tr>
<tr>
<td>2400 lbs.</td>
<td>24 hours</td>
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</tbody>
</table>
Withdrawal Periods

- Xylazine- FARAD recommends a meat withdrawal period of 4 days and a milk withdrawal period of 24 hours
- Ketamine- Meat and milk withdrawal period is 72 hours
- A reasonable withdrawal time for opiates in cattle of at least 48 hours has been suggested in the literature.
Drug Analysis

- Plasma xylazine, ketamine and butorphanol concentrations determined by LC-MS
- Analytical range of 0.5 - 100 ng/mL
- Plasma salicylate determined by fluorescence polarization immunoassay
- Analytical range of 5 μg/mL - 800 μg/mL
Data Analysis

- Pharmacokinetic parameters were determined by non-compartmental analysis (NCA).
- Calves were classified as pain; no-pain; NSAID or no NSAID.
- PK parameters were compared for each classification using a mixed effects model with calf (treatment) designated as a random effect.
Results

- Plasma salicylate results at dehorning following inclusion of sodium salicylate in the drinking water ranged from 11.5 to 78.7 μg/mL in Period 1 and 8.9 to 92.9 μg/mL in Period 2.
- Inclusion of sodium salicylate decreased water intake in the treated groups.
Plasma Salicylate concentrations

Log Plasma Sodium Salicylate Concentration (μg/mL)

Time from initial sodium salicylate administration (day -3) (h)

30 μg/mL
Salicylate consumption in the drinking water over time
Does pain alter the pharmacokinetics of sedative-analgesic drugs administered IM?
Mean plasma xylazine concentrations (ng/ml) following co-administration of xylazine (0.05mg/kg), ketamine (0.1 mg/kg) and butorphanol (0.025 mg/kg) IM and sodium salicylate prior to sham dehorning/castration, actual dehorning/castration in calves.
Mean plasma ketamine concentrations (ng/ml) following co-administration of xylazine (0.05mg/kg), ketamine (0.1 mg/kg) and butorphanol (0.025 mg/kg) IM and sodium salicylate prior to sham dehorning/castration, actual dehorning/castration in calves.
Conclusions

- Pain associated with dehorning and castration appeared to increase the peak plasma xylazine concentration ($p = 0.04$).
- Inclusion of sodium salicylate in the drinking water tended to increase the half-life of xylazine but the effect was not statistically significant ($p=0.1$).
- The area under the concentration time curve was significantly less in the group not receiving the NSAID or experiencing pain.
What effect did the drugs have on markers of pain and distress
Sham Phase
Castration and Dehorning
Can sustained analgesia have a performance effect?

![Bar chart showing ADG (kgs) for different treatment groups: Control, SAL, XKB, XKB + SAL. The chart indicates varying levels of ADG across groups.](diagram)
Is there something we can use that may work better than Sodium Salicylate?

- Meloxicam tablets have 100% oral bioavailability
- Human generic tablets cost 4c/15mg tab or $0.20/100 lbs
- Oral meloxicam at 1mg/kg has a half-life of 27 hours
- EU meat withdrawal period is 15 days (0.5 mg/kg IM) and Canadian withdrawal is 20 days
Pharmacokinetics of oral meloxicam in calves

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Calf 16</th>
<th>Calf 18</th>
<th>Calf 23</th>
<th>Calf 31</th>
<th>Calf 40</th>
<th>Calf 44</th>
<th>Mean</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
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<tbody>
<tr>
<td>$\text{AUC}_{\text{EXTRAPOLATED}}$</td>
<td>%</td>
<td>23.01</td>
<td>30.01</td>
<td>39.43</td>
<td>4.14</td>
<td>5.85</td>
<td>33.02</td>
<td>16.71</td>
<td>4.14</td>
<td>26.51</td>
<td>39.43</td>
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<tr>
<td>$\text{AUC}_{\text{INF}}$</td>
<td>hr*ug/mL</td>
<td>295.80</td>
<td>129.03</td>
<td>153.46</td>
<td>140.60</td>
<td>153.18</td>
<td>156.84</td>
<td>164.46</td>
<td>129.03</td>
<td>153.32</td>
<td>295.60</td>
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<tr>
<td>$\text{AUMC}_{\text{INF}}$</td>
<td>hr<em>hr</em>ug/mL</td>
<td>19736.82</td>
<td>5205.64</td>
<td>8017.42</td>
<td>4730.72</td>
<td>6087.68</td>
<td>6837.34</td>
<td>7384.86</td>
<td>4730.72</td>
<td>6462.51</td>
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<td>$\text{Cl/F}$</td>
<td>mL/min/kg</td>
<td>0.06</td>
<td>0.13</td>
<td>0.11</td>
<td>0.12</td>
<td>0.11</td>
<td>0.11</td>
<td>0.10</td>
<td>0.06</td>
<td>0.11</td>
<td>0.13</td>
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<tr>
<td>$\text{C}_{\text{MAX}}$</td>
<td>ug/mL</td>
<td>3.79</td>
<td>2.93</td>
<td>2.64</td>
<td>3.33</td>
<td>2.83</td>
<td>3.19</td>
<td>3.10</td>
<td>2.64</td>
<td>3.06</td>
<td>3.79</td>
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<td>$\text{T}_{1/2\text{AZ}}$</td>
<td>hr</td>
<td>43.29</td>
<td>24.85</td>
<td>34.10</td>
<td>19.97</td>
<td>21.41</td>
<td>27.83</td>
<td>27.54</td>
<td>19.97</td>
<td>26.34</td>
<td>43.29</td>
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<td>$\text{AZ}$</td>
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<td>0.016</td>
<td>0.028</td>
<td>0.020</td>
<td>0.035</td>
<td>0.032</td>
<td>0.025</td>
<td>0.025</td>
<td>0.016</td>
<td>0.026</td>
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<td>MRT</td>
<td>hr</td>
<td>66.72</td>
<td>40.35</td>
<td>52.24</td>
<td>33.65</td>
<td>39.74</td>
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<td>11.64</td>
<td>10.00</td>
<td>12.00</td>
<td>12.00</td>
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<tr>
<td>$\text{Vz/F}$</td>
<td>L/kg</td>
<td>0.211</td>
<td>0.278</td>
<td>0.321</td>
<td>0.205</td>
<td>0.202</td>
<td>0.256</td>
<td>0.242</td>
<td>0.202</td>
<td>0.234</td>
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<td>MAT</td>
<td>hr</td>
<td>39.81</td>
<td>8.77</td>
<td>22.70</td>
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<td>10.14</td>
<td>16.19</td>
<td>15.07</td>
<td>8.77</td>
<td>13.17</td>
<td>39.81</td>
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<tr>
<td>$\text{F}$</td>
<td></td>
<td>1.66</td>
<td>0.64</td>
<td>0.92</td>
<td>0.97</td>
<td>0.96</td>
<td>1.08</td>
<td>1.00</td>
<td>0.64</td>
<td>0.97</td>
<td>1.66</td>
</tr>
</tbody>
</table>

Pharmacokinetics of meloxicam, 1 mg/kg PO, in cattle
Meloxicam alone does not mitigate the acute cortisol response
Performance benefits?
Mean Average Daily Gain (ADG) (Kg) (+/- SEM) over 10 days in Holstein calves following meloxicam or placebo administration at prior to dehorning (p=0.0365)

But it may offer long term benefits….
Reduced Incidence of BRD?
Incidence of BRD in bulls receiving placebo (74 bulls) or Meloxicam (n=71) 24h prior to castration

a - b: p=0.04
Incidence of BRD in steers receiving placebo (55 steers) or Meloxicam (n=58 steers) 24h prior to processing

BRD Incidence (%)

Meloxicam

Placebo

Group

a - b: p=0.15
Is there something else we can use to treat chronic pain in cattle?

- Gabapentin is a GABA analogue developed to treat epilepsy
- Used to treat chronic and neuropathic pain in humans
- Binds to voltage gated calcium channels (2 μg/mL)
- Decrease excitatory neurotransmitters
- Synergism with NSAIDs
Pharmacokinetics of gabapentin administered at 15 mg/kg PO to ruminant calves
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Geometric Mean</th>
<th>Min</th>
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<td>AUC extrapolated</td>
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<td>0.6</td>
<td>1.1</td>
<td>4.4</td>
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<tr>
<td>AUC</td>
<td>hr*μg/mL</td>
<td>67.62</td>
<td>37.05</td>
<td>71.03</td>
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<tr>
<td>AUMC</td>
<td>hr<em>hr</em>μg/mL</td>
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<td>Cl/F</td>
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<td>CMAX</td>
<td>μg/mL</td>
<td>3.4</td>
<td>1.7</td>
<td>3.7</td>
<td>4.6</td>
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<tr>
<td>T ½</td>
<td>hr</td>
<td>7.9</td>
<td>6.9</td>
<td>7.4</td>
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<td>16.9</td>
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<td>TMAX</td>
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<tr>
<td>Vz/F</td>
<td>L/kg</td>
<td>2.54</td>
<td>1.68</td>
<td>2.13</td>
<td>7.22</td>
</tr>
</tbody>
</table>
Total steps taken following lameness induction with amphoterecin B and four treatments with meloxicam (0.5 mg/kg PO q24h) alone or in combination with gabapentin (15 mg/kg PO q 24h)

Different Symbols p<0.05
Force (Raw Sum) following lameness induction with amphoterecin B and four treatments with meloxicam (0.5 mg/kg PO q24h) alone or in combination with gabapentin (15 mg/kg PO q 24h)

Different Symbols p<0.05
Length of the stride (cm) following lameness induction with amphoterecin B and four treatments with meloxicam (0.5 mg/kg PO q24h) alone or in combination with gabapentin (15 mg/kg PO q 24h)
How do we “sell” animal welfare to our clients?

Can we get ahead of the game?
Making welfare research relevant to producers

- It’s the right thing to do……..
- Growth and performance benefits
  - May be short lived but “return to feed” may have some upside
- Reduced incidence of BRD?
- Food Safety implications?
- Get ahead of any future welfare issue
"And I'm telling you it is not the same ... it's definitely greener on the other side. I say we switch tables."

EAT BEEF
THE WEST WASN'T WON ON SALAD