INTRODUCTION + RATIONALE

Current equine pain management involves mostly non-steroidal anti-inflammatory drugs (NSAIDs) and α2 adrenergic agonists.

Opioids used sparingly in horses due to commonly seen adverse effects.

Inflammation of the synovial fluid (synovitis) involves mostly non-steroidal anti-inflammatory drugs (NSAIDs).

Increased analgesic options needed to improve patient care.

Decreased gastrointestinal motility.

Neuroexcitation.

To the best of our knowledge, first study evaluating analgesic effect of codeine.

Previously published studies showed no adverse effects.

Codeine in horses.

Limited number of studies evaluating the pharmacologic effects.

CODEINE METABOLISM

- Codeine
- Codeine-6-glucuronide
- Norcodeine
- Morphine
- Morphine-3-glucuronide
- Morphine-6-glucuronide
STUDY OBJECTIVE

Specific Aim 1: Describe the pharmacokinetics of codeine and metabolites, including morphine, morphine-6-glucuronide, and morphine-3-glucuronide.

Specific Aim 2: Describe pharmacodynamic effects, including anti-nociceptive and adverse effects following oral administration of codeine to horses.

Oral codeine administration will provide predictable, time-related blood concentrations of parent drug and active metabolites and increase thermal nociceptive threshold with minimal adverse effects.
STUDY DESIGN

- Randomized, balanced crossover design with 7 healthy horses
- Three oral codeine doses (0.3, 0.6, and 1.2 mg/kg), oral saline (negative control), IV morphine (0.2 mg/kg) (positive control)
- Fasting 12 hours prior and 2 hours post-drug administration
- PK data: blood samples up to 72 hours post-drug administration
- Using LC-MS/MS for concentration determination
- Step counts
- Effect on thermal threshold
- Defecation incidence and consistency
- Gastrointestinal borborygmi
- Heart rate and rhythm
- Behavioral observation
- Step counts
- Defecation incidence and consistency
- Gastrointestinal borborygmi
- Heart rate and rhythm
- Behavioral observation
- Randomized, balanced crossover design with 7 healthy horses
%TE = 100 \times \left(\frac{T_T - T_0}{T_C - T_0}\right),

\begin{itemize}
  \item $T_T=$thermal nociceptive cut-off temperature
  \item $T_0=$skin temperature
  \item $T_C=$thermal nociceptive cut-off temperature
  \item $T_T=$thermal threshold
  \item $T_0=$thermal threshold
\end{itemize}

METHODS- THERMAL EXCLUSION

TopCat Metrology UK device
### RESULTS - PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose Groups</th>
<th>Units</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cmax (ng/mL)</strong></td>
<td>0.3mg/kg (n=3)</td>
<td>3.27 ± 2.43</td>
<td>268.3 ± 158.7</td>
</tr>
<tr>
<td></td>
<td>0.6mg/kg (n=3)</td>
<td>2.38 ± 1.13</td>
<td>277.7 ± 112.6</td>
</tr>
<tr>
<td></td>
<td>1.2mg/kg (n=3)</td>
<td>0.341 ± 0.168</td>
<td>427.8 ± 233.8</td>
</tr>
<tr>
<td><strong>Tmax (h)</strong></td>
<td>0.3mg/kg (n=3)</td>
<td>0.967 ± 0.44</td>
<td>0.583 ± 0.382</td>
</tr>
<tr>
<td></td>
<td>0.6mg/kg (n=3)</td>
<td>0.983 ± 0.382</td>
<td>0.583 ± 0.144</td>
</tr>
<tr>
<td></td>
<td>1.2mg/kg (n=3)</td>
<td>0.968 ± 0.42</td>
<td>0.667 ± 0.289</td>
</tr>
<tr>
<td><strong>Lambda Z (1/h)</strong></td>
<td>0.3mg/kg (n=3)</td>
<td>0.341 ± 0.164</td>
<td>0.341 ± 0.164</td>
</tr>
<tr>
<td></td>
<td>0.6mg/kg (n=3)</td>
<td>0.218 ± 0.158</td>
<td>0.218 ± 0.158</td>
</tr>
<tr>
<td></td>
<td>1.2mg/kg (n=3)</td>
<td>0.258 ± 0.129</td>
<td>0.258 ± 0.129</td>
</tr>
<tr>
<td><strong>HL Lambda Z (h)</strong></td>
<td>0.3mg/kg (n=3)</td>
<td>2.38 ± 1.13</td>
<td>2.38 ± 1.13</td>
</tr>
<tr>
<td></td>
<td>0.6mg/kg (n=3)</td>
<td>4.30 ± 2.43</td>
<td>4.30 ± 2.43</td>
</tr>
<tr>
<td></td>
<td>1.2mg/kg (n=3)</td>
<td>3.27 ± 1.13</td>
<td>3.27 ± 1.13</td>
</tr>
<tr>
<td><strong>AUC 0-Inf (h*ng/mL)</strong></td>
<td>0.3mg/kg (n=3)</td>
<td>343.0 ± 159.4</td>
<td>343.0 ± 159.4</td>
</tr>
<tr>
<td></td>
<td>0.6mg/kg (n=3)</td>
<td>356.8 ± 160.6</td>
<td>356.8 ± 160.6</td>
</tr>
<tr>
<td></td>
<td>1.2mg/kg (n=3)</td>
<td>543.9 ± 190.2</td>
<td>543.9 ± 190.2</td>
</tr>
</tbody>
</table>

- **Cmax** = maximum measured concentration;
- **Tmax** = time of maximum concentration;
- **Lambda Z** = terminal slope; **HL Lambda Z** = terminal half-life;
- **AUC 0-Inf** = area under the plasma concentration curve from time 0 to infinity.
RESULTS - CONCENTRATIONS
RESULTS

Thermal Exclusion

Time (hrs)

% Thermal Exclusion

- 0 mg/kg Morphine IV (n=6)
- 1 mg/kg Codeine PO (n=5)
- Saline PO (n=4)
RESULTS - STEP COUNTS
ADDITIONAL RESULTS

- Neuroexcitation seen post-morphine administration, no change in heart rate observed with codeine doses.
- Increased heart rate seen post-morphine administration, no change in heart rate.
- Preliminary results suggest a decrease in GI sounds over the first two hours post-drug administration for 1.2 mg/kg codeine dose and morphine (positive control).
- Increased heart rate seen post-morphine administration, no significant adverse behavioral effects observed with increased steps.
- All three codeine doses and morphine appeared to cause a decrease in defecation incidence over the first six hours post-drug administration before returning to baseline.
- Increased heart rate seen post-morphine administration.
CONCLUSIONS

• Concentrations of morphine metabolites were equivalent to or exceeded those observed following administration of an analgesic dose of morphine (0.2 mg/kg IV).

• Thermal nociceptive data collected thus far suggest codeine may have similar analgesic properties to morphine (0.2 mg/kg IV).

• No significant adverse behavioral effects observed following codeine administration.

• Further research to explore analgesic properties of codeine in horses warranted.

• Potential use as an analgesic in equine patients is promising.

• Concentrations of morphine metabolites were equivalent to or exceeded those observed following administration of all three codeine doses.
ACKNOWLEDGEMENTS

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QUESTIONS?