Pharmacokinetics, Adverse Effects, and Effect on Thermal Nociception of Codeine following Administration of 3 Doses to Horses

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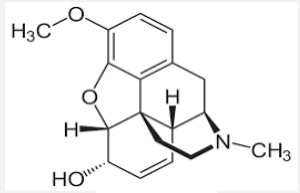
UCDAVIS
VETERINARY MEDICINE

INTRODUCTION+ RATIONALE

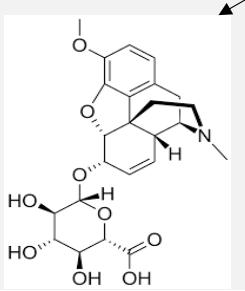
- Current equine pain management involves mostly non-steroidal anti-inflammatory drugs (NSAIDs) and α_2 adrenergic agonists
- Opioids used sparingly in horses due to commonly seen adverse effects[1]
  - Neuroexcitation
  - Decreased gastrointestinal motility
- Increased analgesic options needed to improve patient care
- Codeine in horses
  - Previously published studies showed no adverse effects[2]
  - Limited number of studies evaluating the pharmacologic effects[3,4]
  - To the best of our knowledge, first study evaluating analgesic effect of codeine

1-Osborne et. Al, *Clin. Pharmacol. Ther* 1990; 2-Gretler et al., *Vet Anaesth. and Analg.,* 2020; 3-Stevenson et al., *J. Vet. Pharmacol. Ther.* , 1990; 4-Westermann et al., *Am. J. Vet. Res,* 2005)

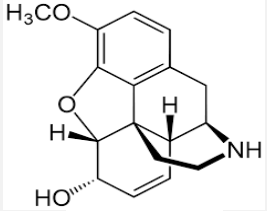
CODEINE METABOLISM



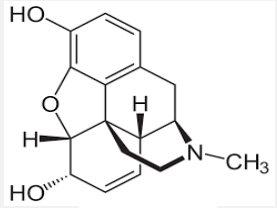
Codeine



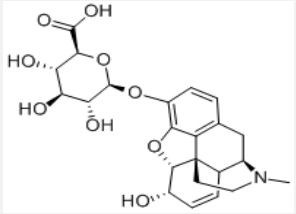
Codeine-6-glucuronide



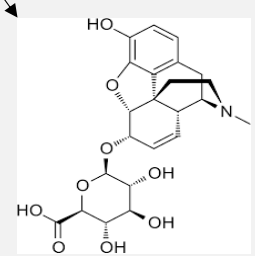
Norcodeine



Morphine



Morphine-3-glucuronide



Morphine-6-glucuronide

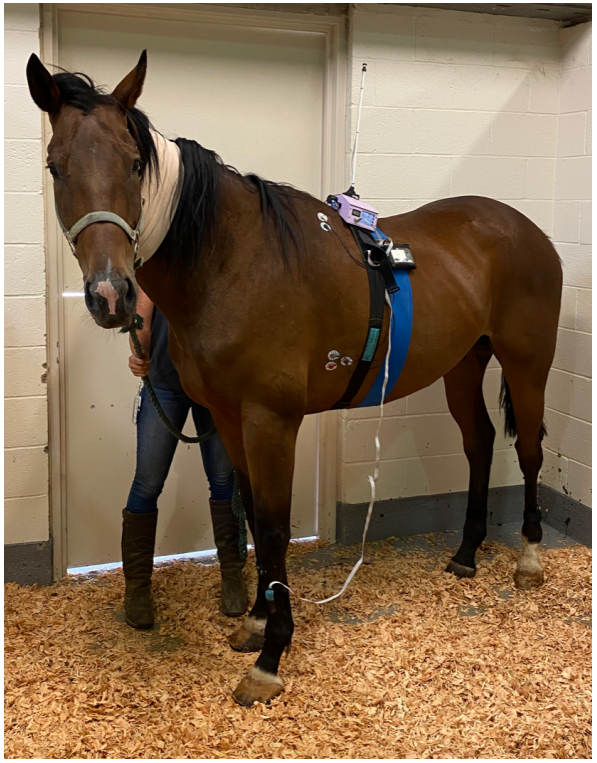
STUDY OBJECTIVE

- **Specific Aim 1:** Describe the pharmacokinetics of codeine and metabolites, including morphine, morphine-6-glucoronide, and morphine-3-glucoronide.
- **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 (0.2mg/kg)(positive control)
- Fasting 12hrs prior and 2hrs post-drug administration
- PK data: blood samples up to 72hrs post-drug administration
  - LC-MS/ MS for concentration determination
- PD data up to 6hrs post-drug administration
  - Effect on thermal threshold
  - Step counts
  - Heart rate and rhythm
  - Gastrointestinal borborygmi
  - Defecation incidence and consistency
  - Behavioral observation



METHODS-THERMAL EXCLUSION

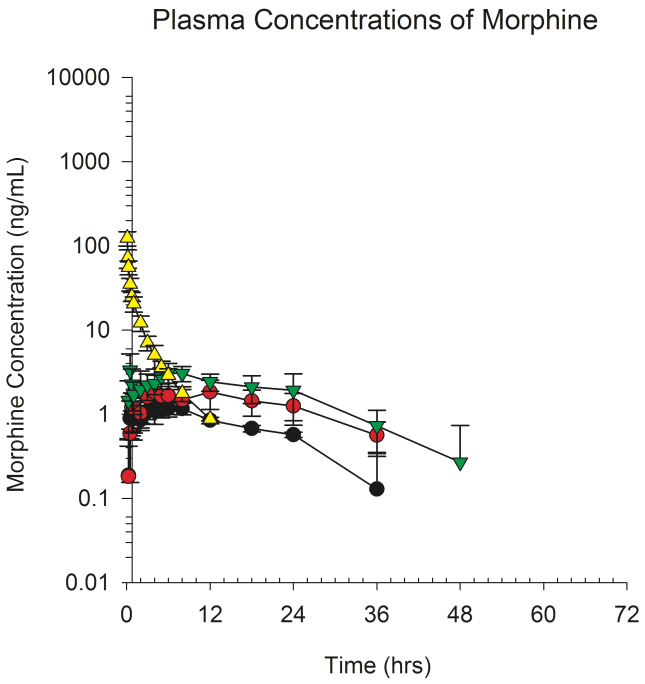
- TopCat Metrology UK device
- %TE = 100 x [$(T_T - T_0)/(T_C - T_0)$],
- T_T=thermal threshold,
- T_0=skin temperature
- T_C=thermal nociceptive cut-off temperature

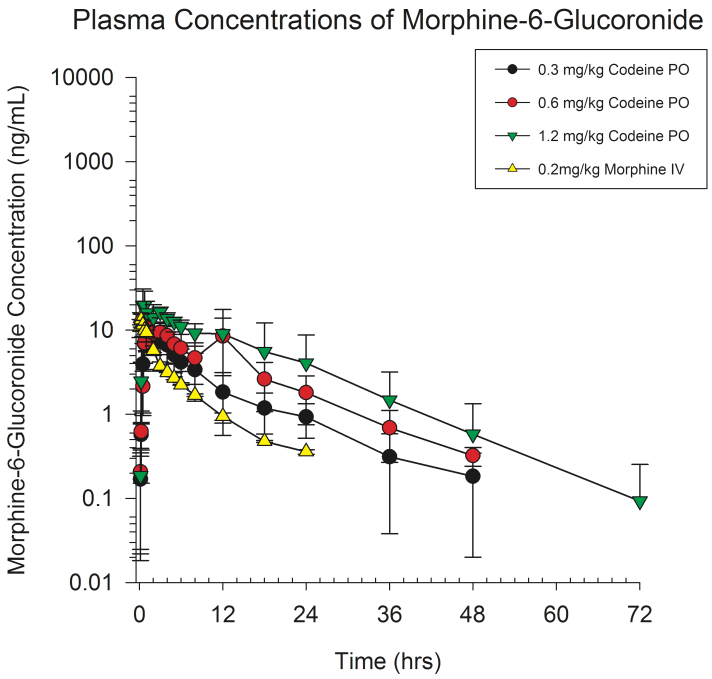
RESULTS - PHARMACOKINETICS

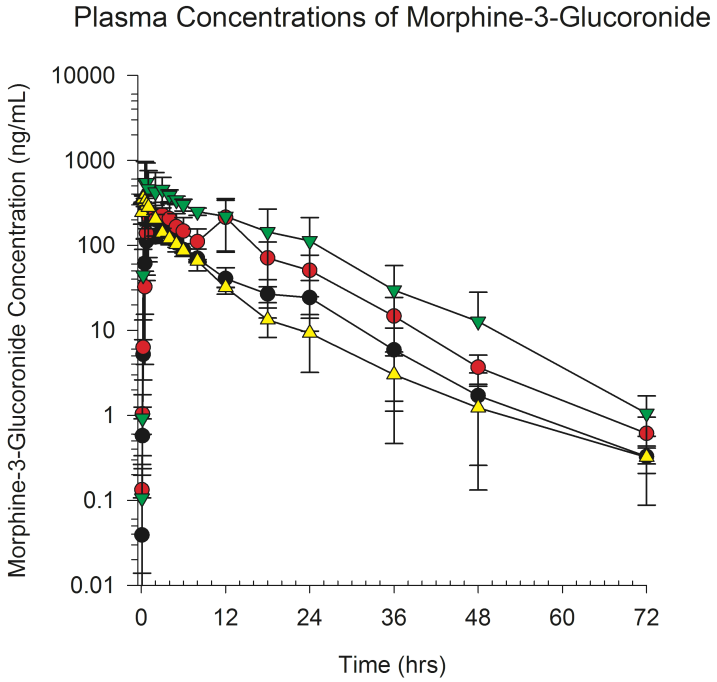
Parameters	Dose Groups		
	0.3mg/kg (n=3)	0.6mg/kg (n=3)	1.2mg/kg (n=3)
C_{max} (ng/mL)	268.3 ± 158.7	277.7 ± 112.6	427.8 ± 233.8
T_{max} (h)	0.583± 0.382	0.583 ± 0.144	0.667± 0.289
$Lambda_Z$ (1/h)	0.341± 0.164	0.218± 0.158	0.258± 0.129
HL $Lambda_Z$ (h)	2.38 ± 1.13	4.30 ± 2.43	3.27 ± 1.83
$AUC_{0\text{-}inf}$(h*ng/mL)	343.0 ± 159.4	356.8 ± 160.6	544.9 ± 153.0

C_{max}=maximum measured concentration; T_{max}=time of maximum concentration; $Lambda_Z$=terminal slope; HL $Lambda_Z$=terminal half-life; $AUC_{0\text{-}inf}$=area under the plasma-concentration curve from time 0 to infinity

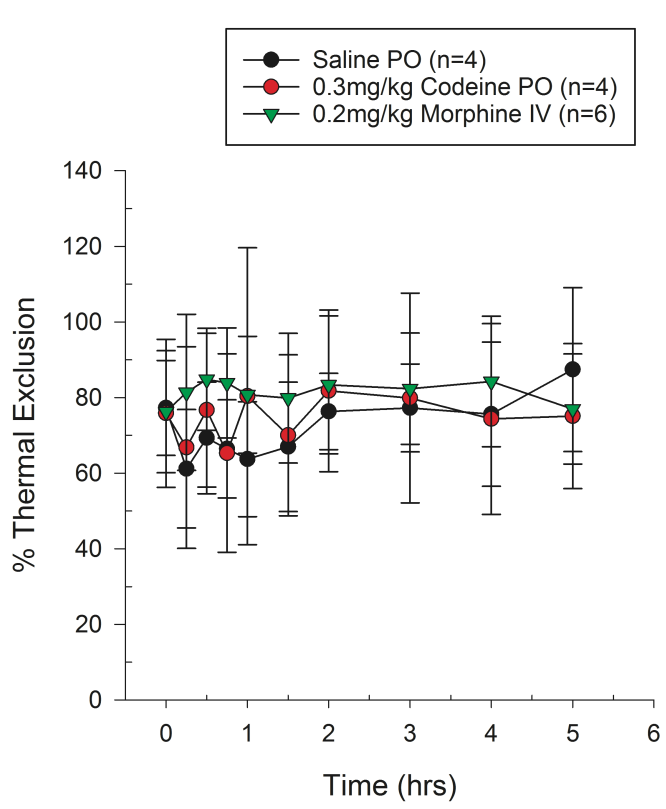
RESULTS- CONCENTRATIONS

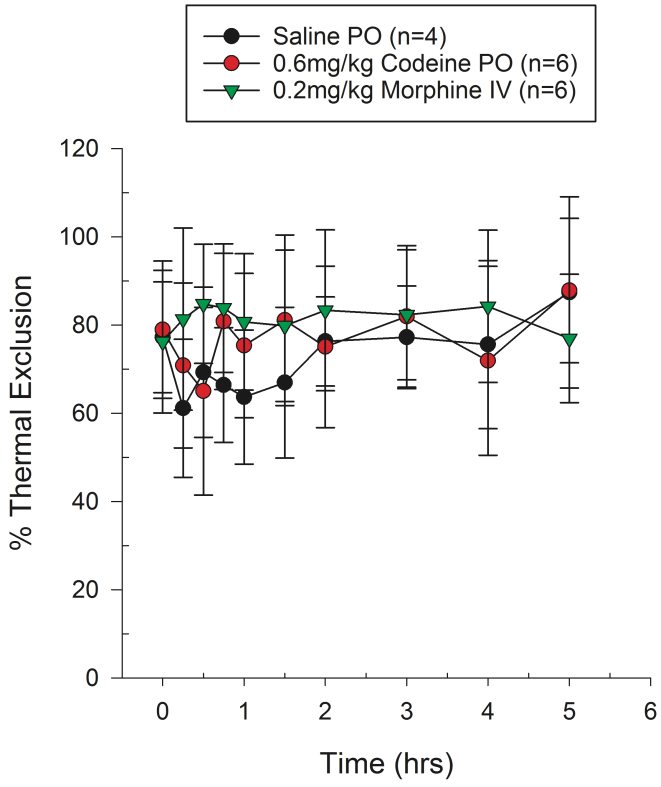


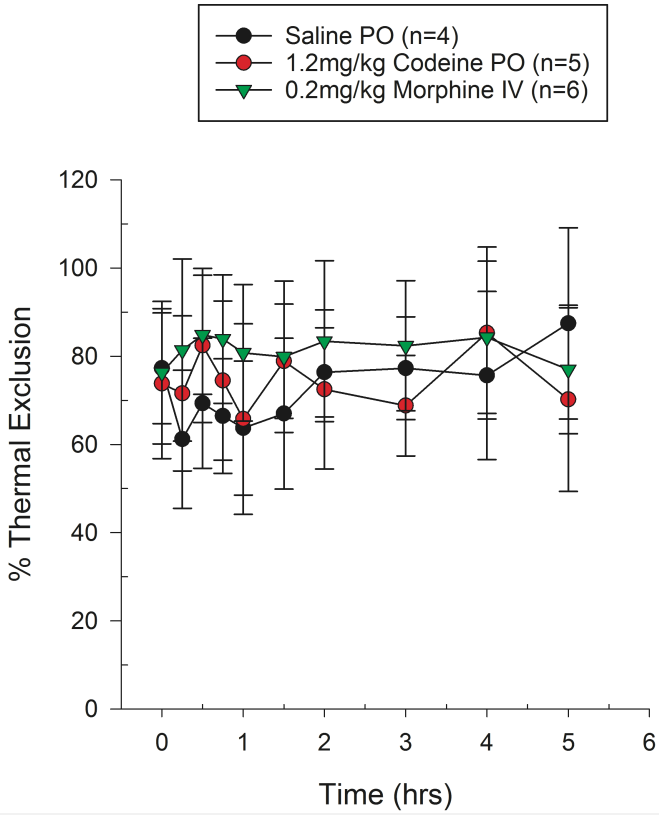




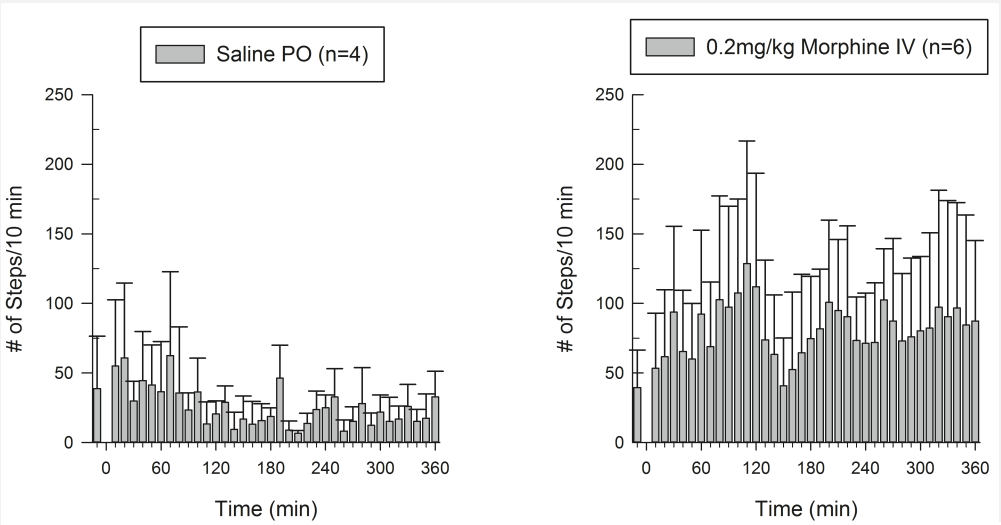
RESULTS-THERMAL EXCLUSION

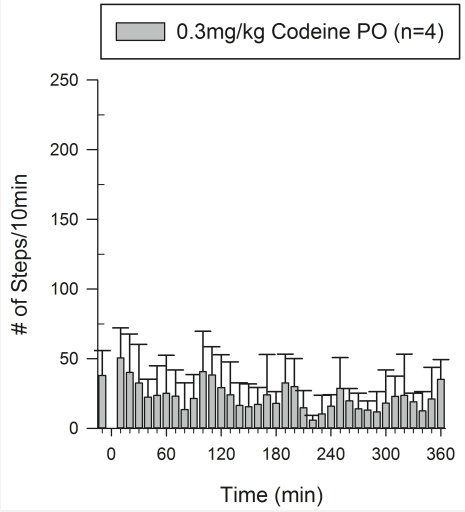


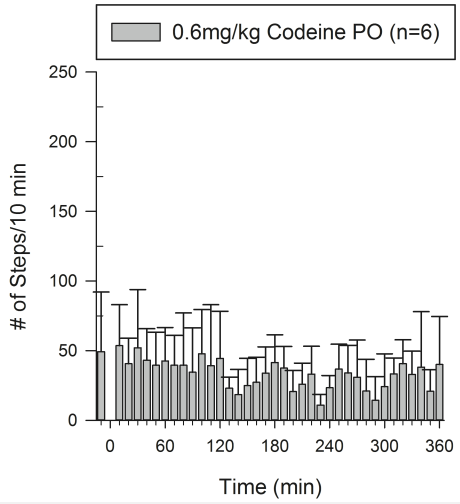


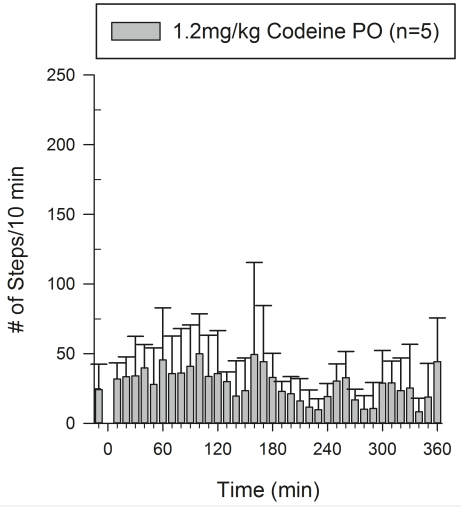


RESULTS- STEP COUNTS









ADDITIONAL RESULTS

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

CONCLUSIONS

- Concentrations of morphine metabolites were equivalent to or exceeded those observed following administration of an analgesic dose of morphine (0.2 mg/kg) following administration of all three codeine doses
- Thermal nociceptive data collected thus far suggests 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 analgesic in equine patients is promising

ACKNOWLEDGEMENTS

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- Mentor: Dr. Heather Knych

QUESTIONS?