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A Tale of Two Metabolites: An Analysis of the Pharmacokinetics of Morphine When Administered Orally

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Introduction

Given the limited analgesic options to relieve equine pain, there exists a need to expand treatment options. Morphine metabolizes into the metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Prior studies have linked M3G to adverse effects of morphine, including neuroexcitation, and M6G to its beneficial analgesic effects. It has also been shown in other species that the route of administration of morphine impacts its metabolism to M6G. This finding lends itself to this study, an exploration of an innovative route of administration for morphine in horses—oral—to determine if this method will yield a greater conversion to M6G compared with IV administration, while minimizing morphine's adverse effects.

Hypothesis

Following oral administration of morphine, M6G will reach higher concentrations than when the drug is administered intravenously and will result in fewer undesirable effects.

Methods

Specific Aim 1: Characterize the metabolism of morphine after oral administration focusing on its conversion to M6G.

- The project was performed in a randomized balanced four-way balanced crossover design with a sample size of 8.
- A single IV administration of 0.2 mg/kg of morphine and an oral administration of 0.2, 0.6, and 0.8 mg/kg of morphine were given to each horse with a minimum two-week washout period between doses.
- Concentrations of morphine, M3G, and M6G were determined from blood samples collected from a jugular vein catheter using a previously published liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Specific Aim 2: Determine the pharmacokinetic parameters of morphine after oral administration.

- The pharmacokinetic properties of morphine after administration were analyzed using a commercially available pharmacokinetic software program (Phoenix Winnonlin v8.2, Certara, Princeton, NJ).

Specific Aim 3: Describe the physiological and behavioral outcomes of morphine when administered orally.

- Such outcomes of morphine were analyzed by assessing the number of steps taken each minute, changes in heart rate, and gastrointestinal borborygmi.

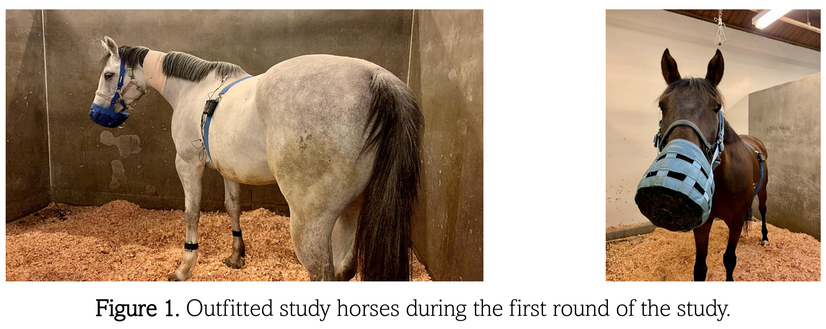

Figure 1. Outfitted study horses during the first round of the study.

Results

Concentrations of M6G and Morphine

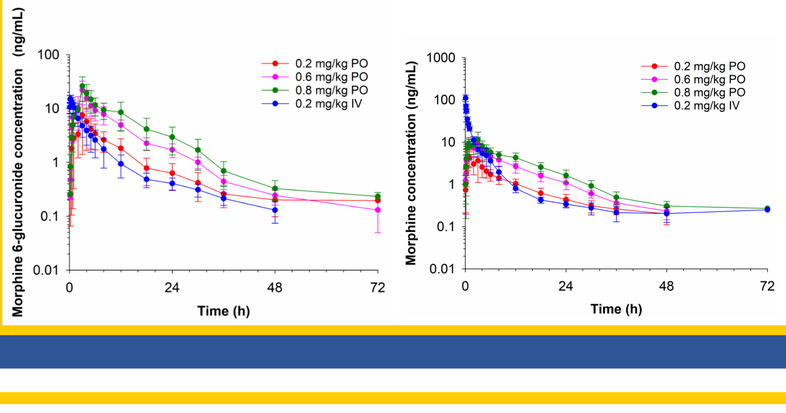

Figure 2. Average concentrations of M6G and morphine over the span of 72 hours.

Results (Continued)

Pharmacokinetic Parameters of Morphine

	0.2 mg/kg PO	0.6 mg/kg PO	0.8 mg/kg PO	0.2 mg/kg IV
C_{max} (ng/mL)	5.32 (2.77-9.16)	10.3 (5.74-15.6)	12.5 (6.19-18.9)	---
C(0) (ng/mL)	---	---	---	168.7 (121.1-237.2)
T_{max} (h)	0.75 (0.5-3.0)	1.5 (0.5-3.0)	1.5 (0.5-3.0)	---
AUC_{inf} (h*ng/mL)	41.6 (33.3-62.2)	94.2 (65.2-128.4)	127.8 (92.7-174.4)	113.9 (95.9-138.6)
Cl (mL/min/kg)	---	---	---	29.3 (24.0-34.8)
Vd_{ss} (L/kg)	---	---	---	12.2 (7.33-38.1)
$Lambda_z$ (1/h)	0.053 (0.038-0.088)	0.072 (0.045-0.096)	0.077 (0.053-0.088)	0.048 (0.014-0.156)
HL $Lambda_z$ (h)	12.5 (7.90-18.5)	9.37 (6.81-15.3)	8.85 (7.90-13.0)	11.2 (4.43-47.9)
F (%)	36.5 (29.3-51.6)	27.6 (18.2-38.8)	28.0 (19.4-38.4)	---

Figure 3. Pharmacokinetic parameters of morphine determined by noncompartmental analysis.

Step Counts

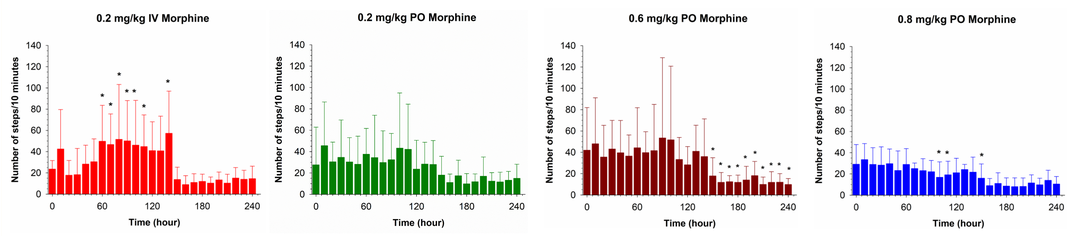

Figure 4. Average number of steps taken from time 0 to 4 hours following administration of morphine. The asterisk (*) represents a statistically significant ($p<0.05$) difference relative to baseline.

Heart Rate

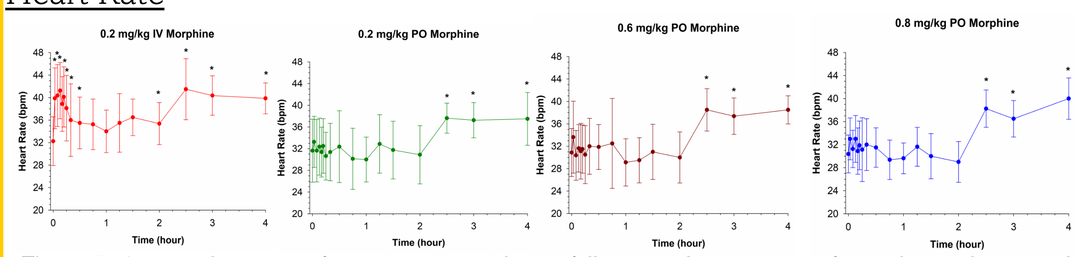

Figure 5. Average heart rate from time 0 to 4 hours following administration of morphine. The asterisk (*) represents a statistically significant ($p<0.05$) difference relative to baseline.

Areas for Further Exploration

Results of the current study are encouraging for further study, specifically the antinociceptive effects of morphine following oral administration.

Acknowledgments

Financial support was provided by the Students Training in Advanced Research (STAR) Program through the NIH T35 OD010956 grant and the Center for Equine Health at the School of Veterinary Medicine, University of California, Davis.

We would also like to extend our sincere gratitude to Kirsten Kanarr, Stacy Steinmetz, Megan Traynham, Tisa Tüshaus, and Sandy Wai-Mun Yim for their invaluable guidance and support.

Citations

1. Klimas R, Mikus G. Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. *Br J Anaesth*. 2014; 113 (6).
2. Knych HK, Steffey EP, McKemie DS. Preliminary pharmacokinetics of morphine and its major metabolites following intravenous administration of four doses to horses. *J Vet Pharmacol Ther*. 2014; 37 (4).