Pharmacokinetics, Pharmacodynamics, & Anti-Nociceptive Effects of Transdermal Buprenorphine Administration in Horses

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INTRODUCTION

Current pain management options available for horses are limited. Opioids, such as buprenorphine, are potent analgesics, but their use in horses is limited by dose-dependent neuroexcitation and adverse gastrointestinal effects. Alternative buprenorphine formulations have been developed over the last several years with the goal of providing sustained analgesia compared to the intravenous formulation. More recently, a transdermal formulation (Zorbium®, Elanco) has been approved for use in cats. This offers several advantages for horses if we can achieve adequate absorption including ease of administration, sustained duration of effect, and continual delivery to the systemic circulation resulting in less fluctuation in drug concentrations that is typically seen with repeated intravenous or intramuscular administration.

HYPOTHESIS

Transdermal buprenorphine administration to horses will result in sustained blood concentrations and anti-nociceptive effects, comparable to those following intravenous administration with less frequent administration, minimal neuroexcitation, and adverse gastrointestinal effects.

METHODS

Specific Aim 1: Describe the plasma concentrations and pharmacokinetics of transdermal buprenorphine

- Randomized four-way balanced crossover design with sample size of 8
- Single topical administration of 15, 30, and 45 µg/kg of buprenorphine and an IV administration of 5 µg/kg of buprenorphine given to each horse with a minimum two-week washout period between doses
- Plasma concentrations of buprenorphine determined using a previously published liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay
- Non-compartmental analysis to generate pharmacokinetic parameters

Specific Aim 2: Describe behavioral, select physiologic, and anti-nociceptive effects following transdermal administration of three doses to horses

- Number of steps taken per minute, changes in heart rate and rhythm, changes in body temperature, and GI motility
- Thermal threshold testing using commercially available wireless device (Topcat Metrology, UK)
- Mechanical nociception assessed using pressure algometer

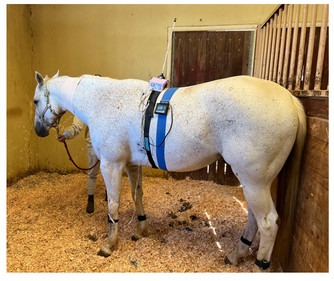

Figure 1. Outfitted study horses for thermal nociception testing, step count, and heart rate monitoring.

RESULTS

Drug Concentrations & Pharmacokinetics:

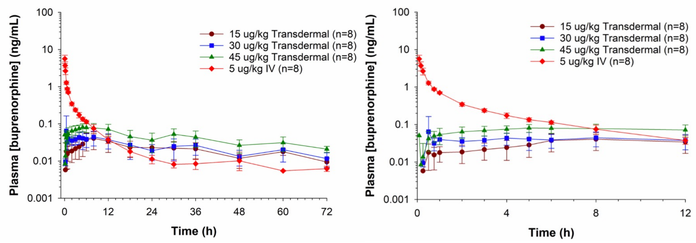

Figure 2. Average plasma concentrations of buprenorphine over 72 hours following transdermal and intravenous administration

	15 µg/kg TD	30 µg/kg TD	45 µg/kg TD	5 µg/kg IV
Cmax (ng/mL)	0.042 ± 0.02	0.076 ± 0.087	0.09 ± 0.02	---
C_0 (ng/mL)	---	---	---	8.28 ± 1.87
Tmax (h)	8 ± 2	3 ± 3.58	5.5 ± 3.4	---
$AUC_{0-\infty}$ (h*ng/mL)	1.55 ± 0.861	2.77 ± 0.784	4.05 ± 2.51	4.69 ± 1.13
HL Lambda$_z$ (h)	18.9 ± 13.2	40.7 ± 15.8	18.8 ± 40.1	10.7 ± 58.3
Lambda$_z$ (1/h)	0.037 ± 0.023	0.017 ± 0.007	0.04 ± 0.05	0.06 ± 0.05
Vss_{obs} L/kg	---	---	---	15.778 ± 20.791

Table 1. Pharmacokinetic parameters for buprenorphine generated by noncompartmental analysis.

Step Counts:

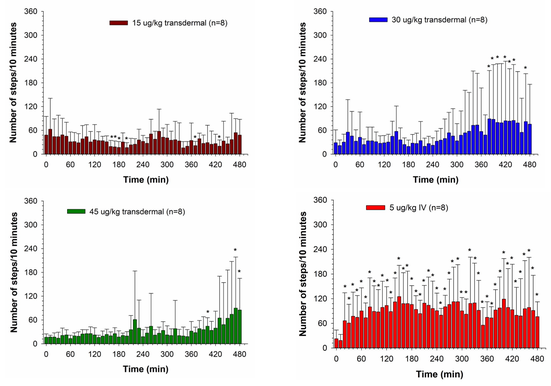

Figure 3. Average number of steps taken from time 0 to 8 hours following buprenorphine administration. The asterisk (*) represents a statistically significant ($p<0.05$) difference relative to baseline.

Heart Rate:

Heart rate was significantly increased, relative to baseline, at 45 minutes post administration in the 15 µg/kg dose group, at 4 and 4.5 hours in the 45 µg/kg dose group, and at 1.25 hours in the IV dose group. Heart rate was significantly decreased in the IV dose group at 10 minutes post administration.

RESULTS (cont.)

GI Motility:

Time (h)	15 ug/kg transdermal	30 ug/kg transdermal	45 ug/kg transdermal	5 ug/kg IV
Baseline	2.4 ± 0.8	2.9 ± 0.8	3.8 ± 0.8	4.3 ± 0.7
0.5	2.6 ± 1.3	2.4 ± 1.1	2.6 ± 0.7*	1.1 ± 1.0*
0.75	2.1 ± 1.5	2.6 ± 0.7	3.4 ± 0.7	1.9 ± 1.5*
1	1.8 ± 1.3	2.0 ± 1.2	3.3 ± 0.7	1.4 ± 1.3*
2	2.1 ± 1.3	2.0 ± 1.1	3.3 ± 0.9	1.6 ± 0.9*
4	2.3 ± 0.5	2.5 ± 1.2	2.9 ± 0.8*	1.6 ± 1.2*
6	2.3 ± 0.7	2.4 ± 1.1	2.6 ± 0.7*	2.4 ± 1.4*
8	2.6 ± 0.7	2.8 ± 1.8	2.8 ± 1.0*	1.8 ± 1.2*
12	2.5 ± 0.9	2.4 ± 0.9	1.9 ± 0.6*	2.3 ± 1.2*
18	2.5 ± 0.9	2.5 ± 0.8	2.9 ± 1.0*	2.9 ± 1.4*
24	3.3 ± 1.3	2.5 ± 0.9	2.1 ± 1.6*	3.0 ± 0.0*
30	3.1 ± 0.8	2.8 ± 1.3	2.5 ± 1.1*	2.6 ± 0.7*
36	2.6 ± 0.9	2.1 ± 1.3	2.9 ± 1.3*	1.9 ± 0.8*
48	3.0 ± 0.8	2.6 ± 0.9	2.9 ± 0.8*	3.0 ± 1.2*
60	2.3 ± 0.7	2.3 ± 1.4	2.8 ± 1.0*	2.6 ± 0.7*
72	2.9 ± 1.1	2.8 ± 0.7	3.1 ± 0.8	2.3 ± 0.9*
84	2.8 ± 0.7	1.3 ± 1.2*	1.5 ± 0.6*	3.1 ± 1.0*

Table 2. Average (+/- SD) gastrointestinal scores from time 0 to 84 hours following buprenorphine administration. The asterisk (*) represents a statistically significant ($p<0.05$) difference relative to baseline.

Thermal nociception:

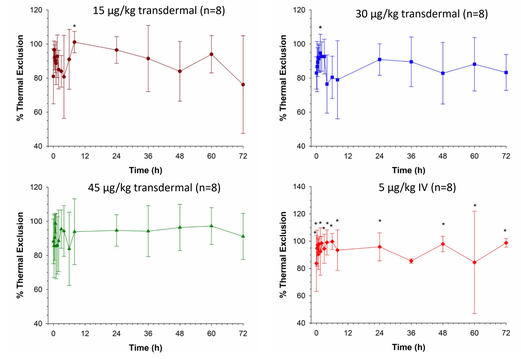

Figure 4. Average thermal exclusion from time 0 to 72 hours following buprenorphine administration. The asterisk (*) represents a statistically significant ($p<0.05$) difference relative to baseline.

Mechanical nociception:

A mechanical anti-nociceptive effect was observed in the 30 µg/kg and IV treatment groups at 1.5 hours post administration.

CONCLUSIONS/FUTURE DIRECTIONS

Plasma concentrations were low for transdermal doses but were well-tolerated. Antinociceptive effects of IV were more apparent than transdermal at doses selected.

The results are encouraging for further studies on analgesic effects of transdermal buprenorphine at different doses and sites of application.

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