Evaluation of Thermal Antinociceptive Effects of Intramuscular Hydromorphone in Great Horned Owls *(Bubo virginianus)*

UCDAVIS VETERINARY MEDICINE
Students Training in Advanced Research

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Introduction

Rationale – Across the Americas, great horned owls are often presented to veterinarians for conditions that require pain management. While recent studies have evaluated the use of opioid drugs in raptor species[1-5], analgesic effects in owls have yet to be investigated.

Opioids - A group of drugs that causes analgesia by reversibly binding to four types of nervous system receptors: μ-opioid, δ-opioid, κ-opioid, & NOP.[6,7]

- **Hydromorphone =** full μ-opioid agonist, morphine derivative with fewer side effects than morphine, commonly used in dogs and cats.[8]
  - Achieved significant thermal antinociception in American kestrels *(Falco sparverius)* for 6 hours at 0.1, 0.3, & 0.6mg/kg (compared to saline).[5]

Hypothesis – Intramuscular administration of hydromorphone would cause a significant dose-dependent increase in the thermal foot withdrawal threshold in great horned owls and will provide analgesia for 3-6 hours.

Materials & Methods

Thermal Withdrawal Threshold - A measure of antinociception defined as the temperature at which the animal lifts its foot (a pain response).

- Thermal stimulus analgesiometry has been validated as reliable and ethical in many species.[9]

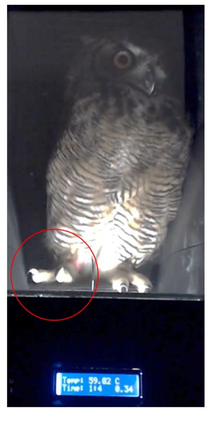
Study Design - A randomized, blinded, and balanced complete crossover

- 6 adult great horned owls (1 male, 5 females)
- Treatments: Hydromorphone at 0.3 & 0.6mg/kg, saline at 0.33mL/kg
- Testing time points: baseline, 0.5, 1.5, 3, & 6 hours
- 7-day washout period between the three testing periods

Left: Test box equipped with three dark sides and a clear front that allows the observer to monitor real-time behavioral responses via a remote video camera. Buttons allow the observer to initiate heating and remove heat (rotate perch 180˚).

Right: View of the box from the inside. The perch is at the bottom of the photo, equipped with a central divider and heating strip where the right foot is placed. The remote camera is at the center of the photo, secured to the wall in front of the clear side of the box.

1. Camera records bird and temperature, observer monitors for behavior changes
2. Metal plate on right half of perch gradually heats up (range: 40-62°C)
3. Thermal threshold = temperature at which bird lifts their foot
4. Observer activates right half of perch to rotate 180°
5. Observer reviews video and records thermal threshold



+3	Owl will not remain on perch and constantly jumps off
+2	Owl intermittently shifts weight or modifies footing but returns to its front facing position on its own, constant panting, looking around
+1	Owl remains still on perch but constantly looks around, pants
0	Owl remains still on perch, is calm, may look around but no panting
-1	Owl reacts mildly to gentle taps on the glass in front of the box
-2	Owl reacts mildly to loud taps on the glass in front of the box
-3	Owl does not react to taps and only reacts when the back of the box is open
-4	Owl is only responsive when touched

Table 1: Agitation-sedation scores, used to assess possible behavioral effects of hydromorphone treatment administered to great horned owls (Bubo virginianus).

Statistical Analysis - completed with R 3.0.1 software. Significance at $p<0.05$.

- Thermal thresholds: Linear mixed modeling with Tukey adjustment
- Sedation scores: ordinal logit mixed model

Results

Thermal Antinociception – Baseline thermal withdrawal thresholds of all birds ranged from 55.8 to 61.8°C. Total standard deviation of the model was 1.9 ˚C. Compared to the control, the 0.6 mg/kg dose resulted in significantly higher mean withdrawal thresholds from 0.5 hours ($p=0.035$) to 1.5 hours ($p=0.001$), while the 0.3mg/kg dose resulted in significantly higher mean withdrawal thresholds from 0.5 hours ($p<0.001$) to 3 hours ($p=0.005$) (Figure 1).

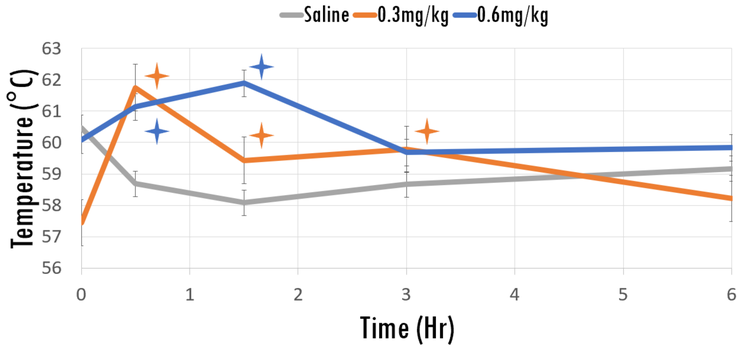


Figure 1: Mean thermal withdrawal threshold values in 6 great horned owls after IM administration of saline and hydromorphone hydrochloride at 0.3 and 0.6mg/kg. Baseline values were measured 5min before IM treatment administration (treatment administration was designated time 0; there was a 7-day interval between treatments). Error bars represent the standard error of the mean.

Sedation - Compared to the control, hydromorphone had a significant effect on sedation at 0.3 and 0.6mg/kg (both P=0.001) (Table 2). This was measured as a decrease in the odds of becoming more alert (quantified by a +1 increase in sedation score). Time did not have a significant effect on sedation.

Treatment (mg/kg)	OR	95% CI	P Value
0.3	0.90	0.02-0.40	0.001
0.6	0.92	0.02-0.33	0.001

Table 2: Proportional odds ratio of different hydromorphone doses compared to saline for increasing the sedation score by 1 (becoming more agitated). OR = proportional odds ratio; CI = confidence interval.

Other Adverse Effects - No other adverse effects (e.g vomiting, diarrhea) were associated with hydromorphone in this study other than two instances of tremoring (after administration of the 0.6mg/kg dose) that did not persist after the 0.5hr timepoint.

Discussion

- Hydromorphone hydrochloride administered IM at 0.3mg/kg and 0.6mg/kg was associated with significant changes in the thermal antinociception threshold, which is suggestive of analgesic effects
  - These results are consistent with findings in American kestrels[5] and orange-winged Amazon parrots[10]
- Hydromorphone caused significant sedation at 0.3 and 0.6mg/kg.
- Compared to saline, the 0.3mg/kg dose of hydromorphone resulted in a longer significant increase in thermal foot threshold than the 0.6mg/kg dose. It is likely that the 0.6mg/kg dose has a longer effect, but the small sample size of this study led to high variability, resulting in type II error. Further studies with a larger sample size are required to better characterize the dose-dependent effect of hydromorphone in these birds.
- As a non-releasable colony, all birds included in this study have previously suffered from injuries or ailments such as wing fractures and ocular disease. While we do not expect this medical history to have an impact on the thermal foot withdrawal threshold, further studies are required to assess the degree to which these historical conditions play a role.

References

1) Guzman DSM, Drazenovich TL, KuKanich B, Olsen GH, Willits NH, Paul-Murphy JR. Evaluation of thermal antinociceptive effects and pharmacokinetics after intramuscular administration of butorphanol tartrate to American kestrels (*Falco sparverius*). American Journal of Veterinary Research; 2014;75(1):11-18
2) Guzman DSM, Drazenovich TL, Olsen GH, Willits NH, Paul-Murphy JR. Evaluation of thermal antinociceptive effects after oral administration of tramadol hydrochloride to American kestrels (*Falco sparverius*). American Journal of Vet Research; 2014;75(2):117-123.
3) Ceulemans SM, Guzman DSM, Olsen GH, Beaufrere H, Paul-Murphy JR. Evaluation of thermal antinociceptive effects after intramuscular administration of buprenorphine hydrochloride to American kestrels (*Falco sparverius*). American Journal of Veterinary Research; 2014;75(8):705-10
4) Guzman DSM, Ceulemans SM, Beaufrere H, Olsen GH, Paul-Murphy JR. Evaluation of the thermal antinociceptive effects of a sustained-release buprenorphine formulation after intramuscular administration to American kestrels (*Falco sparverius*). Journal of Avian Medicine and Surgery; 2018;32(1):1-7.
5) Guzman DS, Drazenovich TL, Olsen GH, Willits NH, Paul-Murphy JR. Evaluation of thermal antinociceptive effects after intramuscular administration of hydromorphone hydrochloride to American kestrels (*Falco sparverius*). American Journal of Veterinary Research; 2013;74(6):817-822.
6) Mansour A, Khachaturian H, Lewis ME, et al. Anatomy of CNS opioid receptors. *Trends in Neurosciences* 1988;11:308-314.
7) Pathan H, Williams J. Basic opioid pharmacology: an update. *British Journal of Pain* 2012;6(1):11-16.
8) Machado CEG, Dyson DH, Grant Maxie M. Effects of oxymorphone and hydromorphone on the minimum alveolar concentration of isoflurane in dogs. *Veterinary Anaesthesia and Analgesia* 2006;33(1):70-77
9) Le Bars D, Gozariu M, Cadden SW. Animal Models of Nociception. *Pharmacological Reviews* 2001;53(4):597-652.
10) Guzman DSM, Douglas JM, Beaufrere H, Paul-Murphy JR. Evaluation of the thermal antinociceptive effects of hydromorphone hydrochloride after intramuscular administration to orange-winged Amazon parrots (*Amazona amazonica*). American Journal of Veterinary Medicine; 2020;81(10):775-782.

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