



Sedation in Great Horned Owls for Non-Invasive Clinical Techniques

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Introduction

Rationale

Reversible, injectable sedation can reduce physiologic signs of stress while mitigating adverse effects commonly encountered with inhalant anesthesia

Drugs

Midazolam (MID) – short-acting benzodiazepine, reversed by flumazenil¹
Dexmedetomidine (DEX) – selective α -2 agonist, reversed by atipamezole¹
Hydromorphone (HYDRO) – full μ -opioid agonist, reversed by naloxone¹

Objectives

Evaluate the following sedation protocols followed by respective reversal agents:

1. MID 2 mg/kg and DEX 0.05 mg/kg IM
2. MID 2 mg/kg and HYDRO 0.6 mg/kg IM
3. MID 2 mg/kg, DEX 0.02 mg/kg, and HYDRO 0.3 mg/kg IM

Each treatment was evaluated for:

- Onset of sedation and onset of recovery, sedation depth and quality
- Adequate sedation for performing non-invasive clinical techniques
- Physiological response to manual restraint

Hypotheses

All three treatments will produce sedation sufficient for:

1. Completion of non-invasive techniques
2. Minimizing physiological response to manual restraint

Materials and Methods

Sedation Depth and Quality

- Time to initial signs of sedation & time to sternal/lateral recumbency
- Sedation scoring

| Criteria | Scoring |
|---|------------------------------------|
| Voluntary Body Movement | Absent (0)/Present (1) |
| Muscle Tremors | Absent (0)/Present (1) |
| Eyelid/Nictitating Membrane Blink | Absent (0)/Present (1) |
| “Whole-head” Nystagmus | Absent (0)/Present (1) |
| Muscle Tone (Leg, Wing, Jaw) ² | None (0) to Marked Response (3) |
| Response to Auditory Stimuli ² | None (0) to Full-body Response (3) |

Tolerance of Clinical Procedures

1. Physical examination
2. Venipuncture
3. Sham radiographic positioning (V/D and LAT)

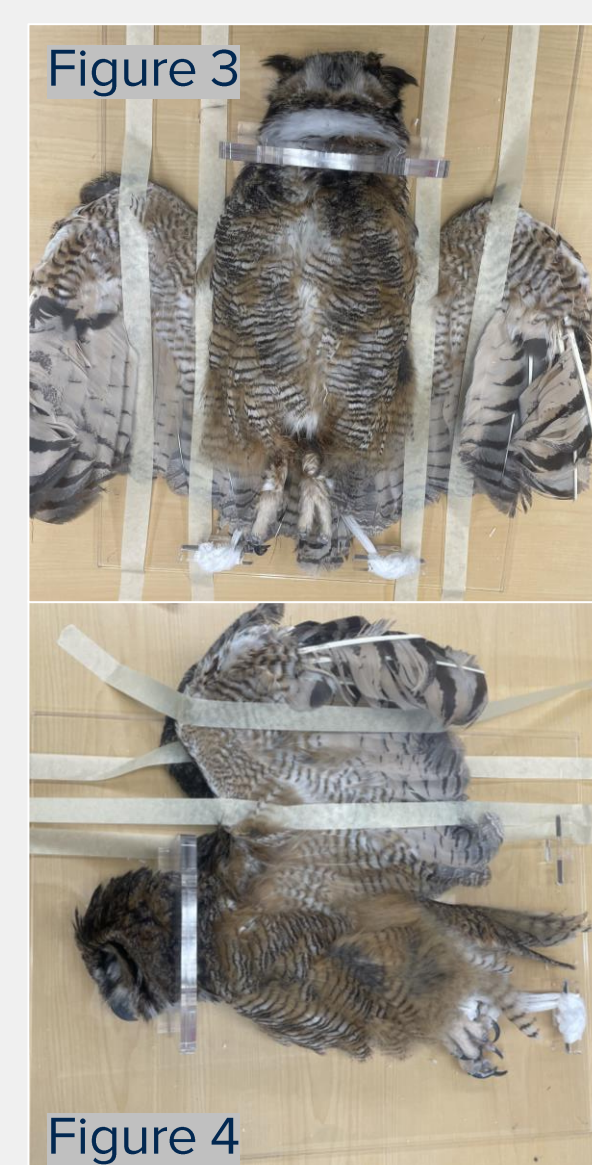
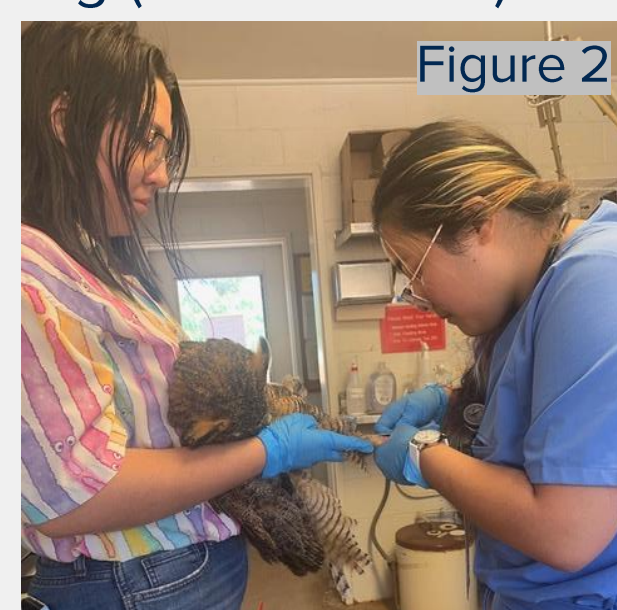
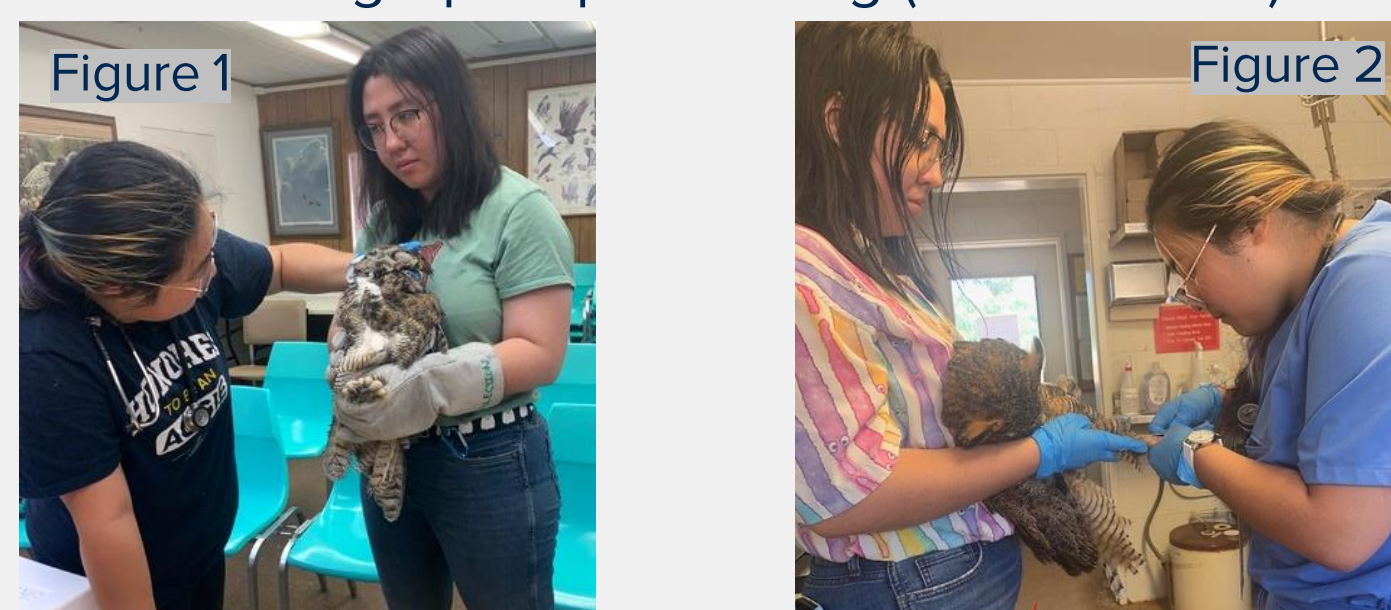


Figure 4

Figure 1: Physical examination. Figure 2: Venipuncture at right medial metatarsal vein. Figure 3: Sham ventrodorsal radiographic positioning. Figure 4: Sham right lateral radiographic positioning.

Physiological Response to Stress

- Respiratory rate (RR) & Heart rate (HR)
- Venous blood gas parameters: pH, pCO₂, pO₂, [glucose], [lactate], acid-base

Recovery

- Time to initial voluntary movement, time to standing posture, & time to full recovery

Crossover Study Design

Great Horned Owls:
n = 6

Sex Distribution:
4 female, 2 male

Age range:
4-25 years old

Mean \pm SD body weight:
1.26 \pm 0.20 kg

History:
Non-releasable birds with chronic orthopedic or visual deficits, healthy based on screening physical exam and bloodwork

Midazolam
2 mg/kg IM
+
Dexmedetomidine
0.05 mg/kg IM

Midazolam
2 mg/kg IM
+
Hydromorphone
0.6 mg/kg IM

Midazolam
2 mg/kg IM
+
Dexmedetomidine
0.02 mg/kg IM
+
Hydromorphone
0.3 mg/kg IM

Week 1

7-day washout

Midazolam
2 mg/kg IM
+
Dexmedetomidine
0.05 mg/kg IM

Midazolam
2 mg/kg IM
+
Hydromorphone
0.6 mg/kg IM

Midazolam
2 mg/kg IM
+
Dexmedetomidine
0.02 mg/kg IM
+
Hydromorphone
0.3 mg/kg IM

Week 2

7-day washout

Midazolam
2 mg/kg IM
+
Dexmedetomidine
0.05 mg/kg IM

Midazolam
2 mg/kg IM
+
Hydromorphone
0.6 mg/kg IM

Midazolam
2 mg/kg IM
+
Dexmedetomidine
0.02 mg/kg IM
+
Hydromorphone
0.3 mg/kg IM

Week 3

Preliminary Results

Figure 5a: Temperature Corrected (104°F) Venous Blood pH

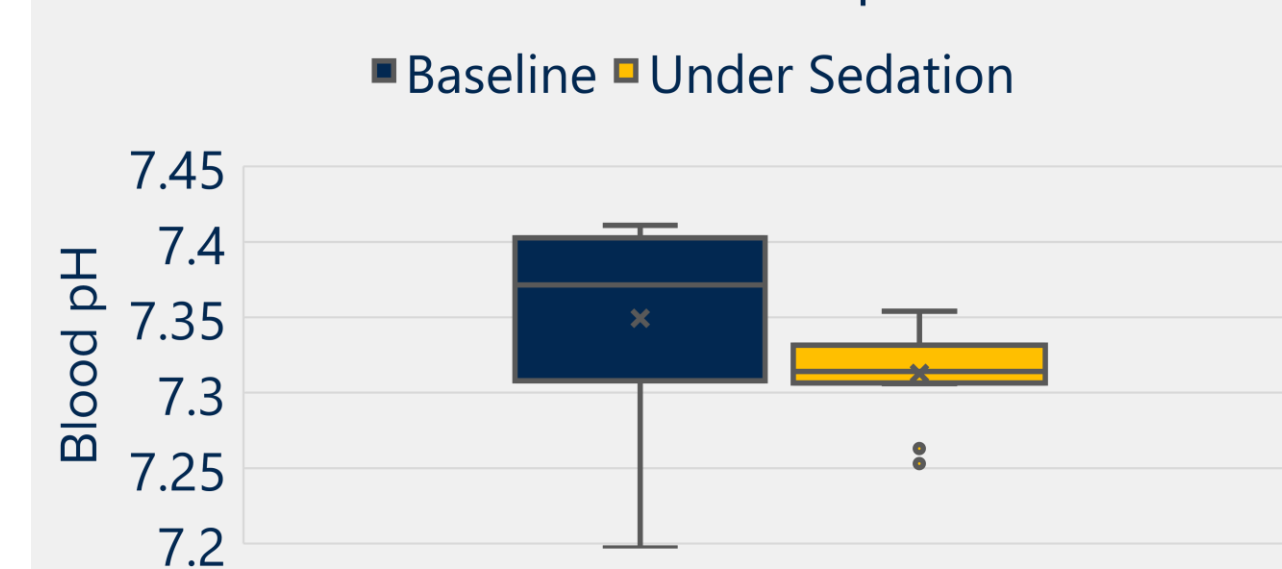


Figure 5: Effect of sedation on ABL800 FLEX values for venous blood in Great Horned Owls from week 1 and 2 trials, with 104°F temperature correction. Box and whisker plots of the (a) pH, (b) pCO₂, (c) pO₂, (d) glucose concentration, and (e) lactate concentration range, median, mean, 1st and 3rd quartiles, and outliers between baseline values and values under sedation.

Figure 6: Table of observed acid-base disorders from baseline, week 1, and week 2 venous blood gas samples. All occurrences outside of avian reference interval³ (7.3-7.5 pH) described.

| Trial Number | Bird ID | Temp. Corr. pH | Acid-Base Eval. | pCO ₂ (mmHg) | [HCO ₃] ⁻ (mmol/L) |
|--------------|-----------|----------------|----------------------|-------------------------|---|
| Baseline | 1999-0192 | 7.197 | Metabolic Acidosis | 31.4 | 11.2 |
| 1 | 2008-0001 | 7.253 | Respiratory Acidosis | 52.0 | 21.2 |
| 2 | 2008-0001 | 7.263 | Respiratory Acidosis | 60.0 | 25.1 |

Figure 5b: Temperature Corrected (104°F) Venous Blood pCO₂

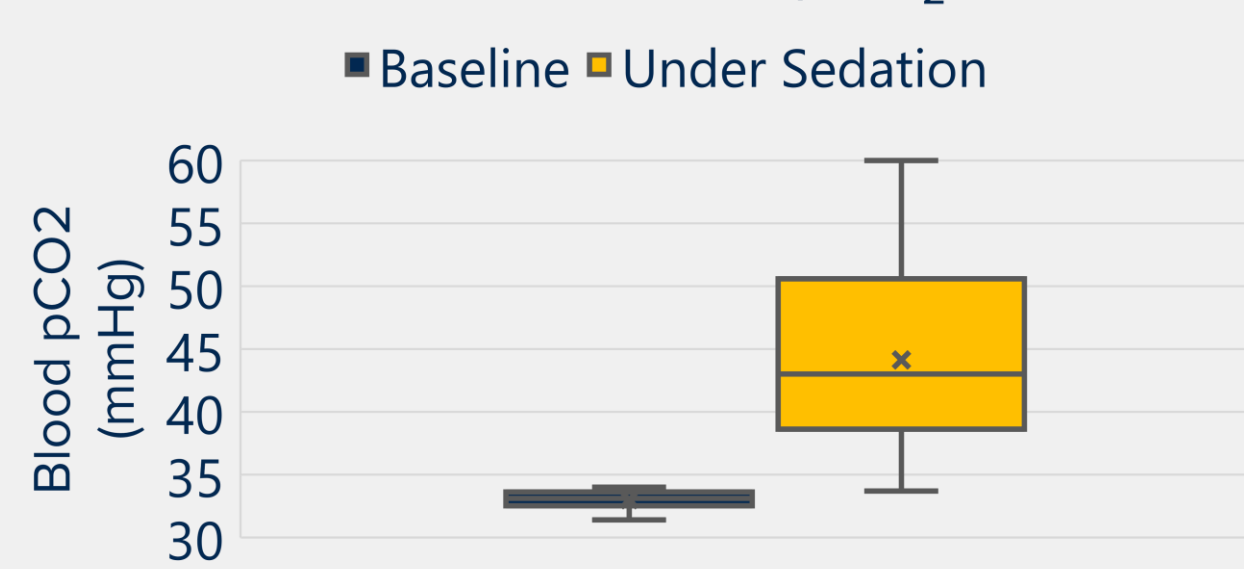


Figure 5d: Venous Blood Glucose Concentrations

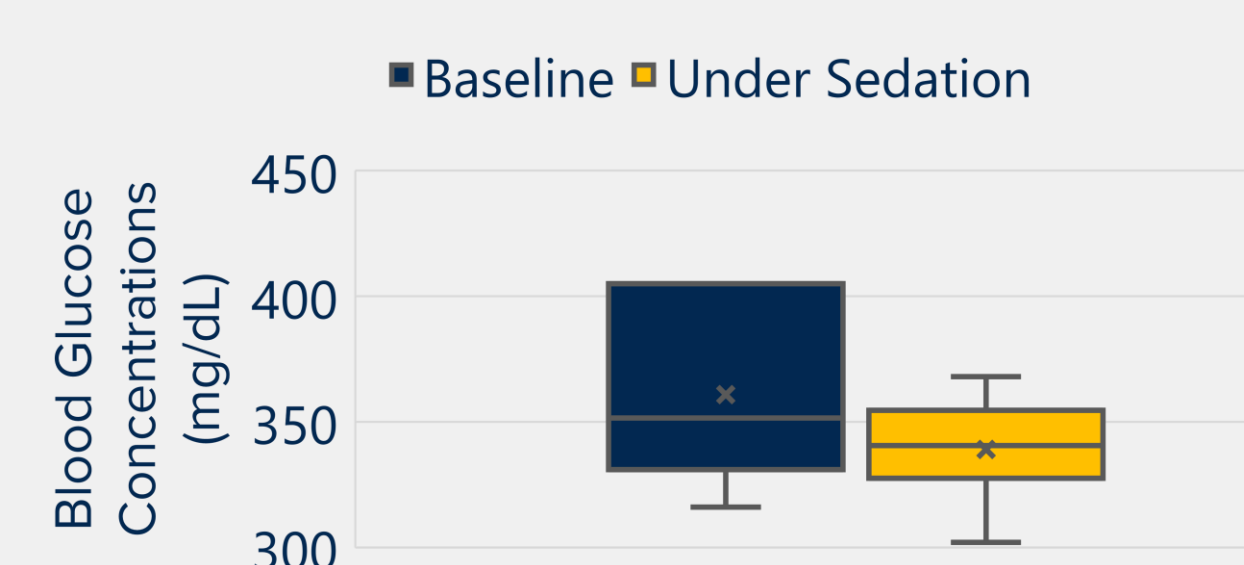


Figure 7: Table of adverse effects observed during sedation trials with definitions and prevalence in trials from week 1 and 2.

| Adverse Effects | Definition | Prevalence |
|---------------------------------|---|-------------------|
| Prolonged recovery | Time to full recovery >4 hours <i>Intervention:</i> 2 nd dose of flumazenil at \geq 1.5-hours post-initial reversal | 75% = 9/12 trials |
| Suspected seizure-like activity | Rhythmic limb extensions, may display opisthotonos | 25% = 3/12 trials |
| Frequent muscle tremors | Tremors present in \geq 3 time points | 25% = 3/12 trials |

Figure 5c: Venous Blood pO₂

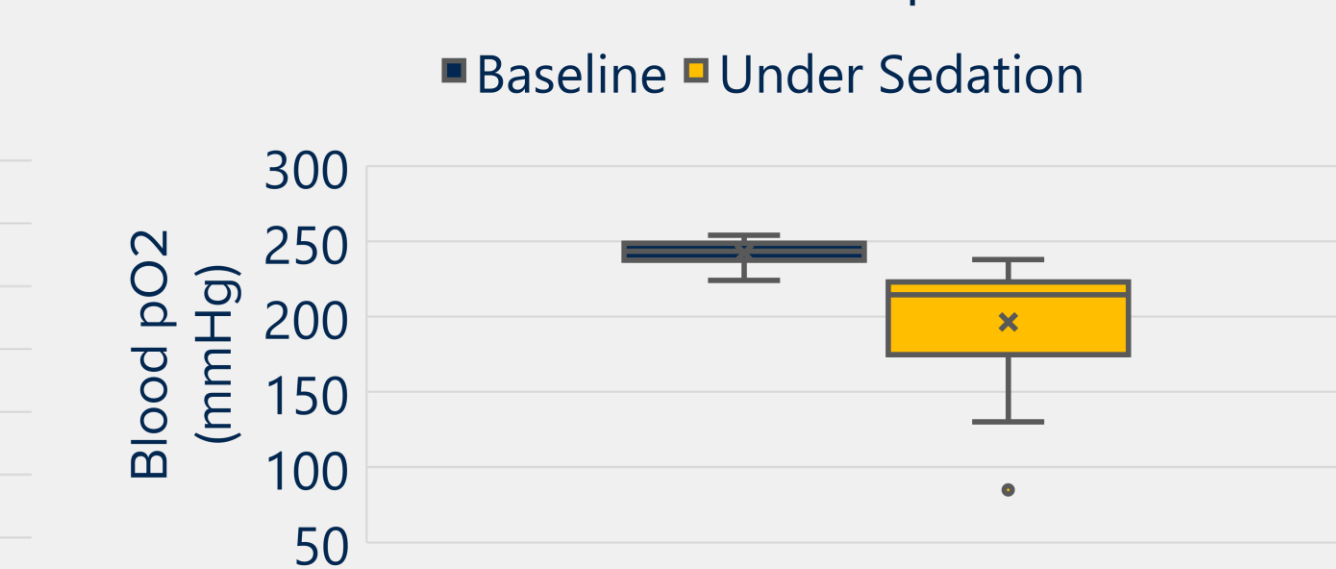
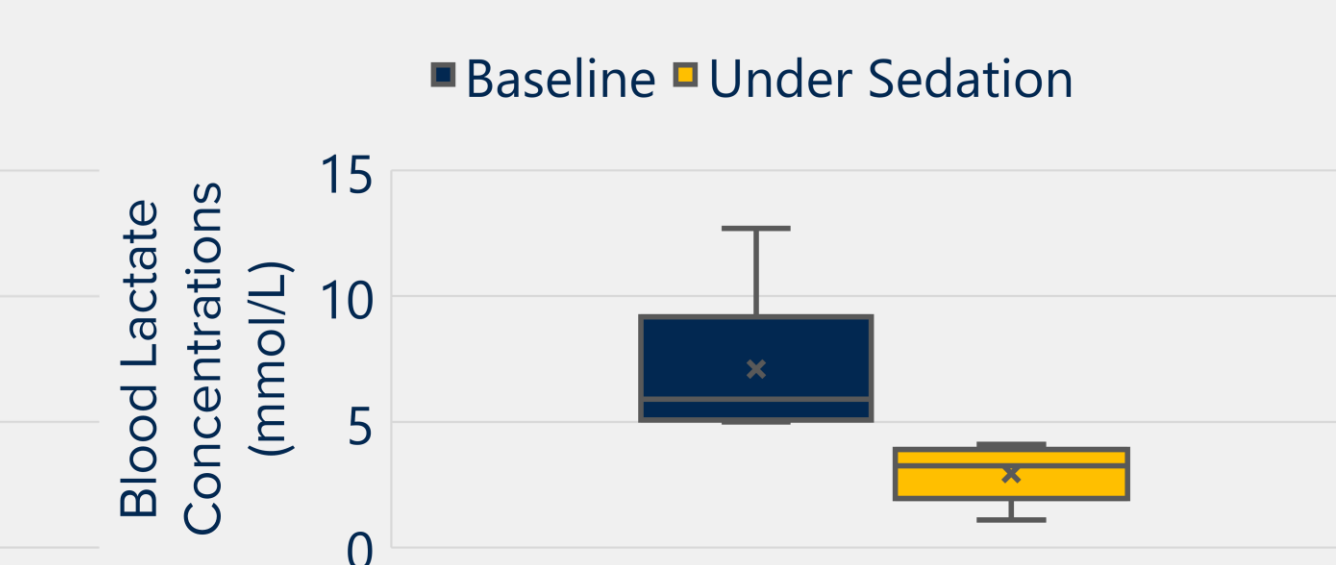


Figure 5e: Venous Blood Lactate Concentrations



In Progress

Control

- High prevalence of adverse effects noted, particularly prolonged recovery
- Untreated control for tolerance of procedures and adverse effects
 - Non-blind, non-randomized control will be compared to treatments

Analysis

Fixed effects: age, sex, treatment order, sedation protocol
Random effect: subject

- Continuous data
 - HR, RR, pH, pCO₂, pO₂, [glucose], [lactate]
 - Linear mixed-effects models
- Binary data
 - Tolerance of V/D and LAT radiographic positioning
 - Logistics mixed-effects models
- Ordinal data
 - Cumulative sedation score
 - Ordinal logistic mixed-effects model

Discussion

Limitations

- High prevalence of prolonged recovery as well cardiorespiratory depression, suspected seizure-like activity and muscle tremors
 - Lack of different sedative dosages and random, blinded control
- Lack of standard sedation scoring in avian pharmacodynamic studies
- Lack of species-specific reference intervals for venous blood gases
- Other physiologic measures of stress not explored:
 - Cloacal temperature and plasma corticosterone concentrations

Future directions

- Pharmacokinetics of MID and DEX in GHOWs
- Pharmacodynamics of MID and DEX as sole agents in GHOWs
- Pharmacodynamics of sedative combinations in other raptor species

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