

URINARY HORMONE CONCENTRATIONS AND PHARMACOKINETICS/PHARMACODYNAMICS OF HALOPERIDOL IN A FEMALE INDIAN RHINOCEROS (*Rhinoceros unicornis*)



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Female Indian Rhino “Manjula”

- DOB 10/25/2005
- Urinary hormone and ultrasound analysis from 12/2009-2/2012 indicated that female should be exhibiting regular estrous cycles
 - 7 follicular phases were observed
 - However, no regular cycles or ovulations were recorded
- Demonstrated periods of acyclicity during the spring and summer of 2010 and 2011



Female Indian Rhino “Manjula”



- Lack of normal estrous cycles due to
 - ✦ Attainment of puberty
 - ✦ Difficulty in acclimating to new surroundings
- Female Indian rhinoceros reach sexual maturity between 4-6 years
- Youngest age at conception in captivity: 2 years and 4 months

Cortisol and Puberty



- Brahman-crossbred heifers (excitable temperament compared to other breeds)
 - ✦ Reach puberty later
 - ✦ Stimulated secretion and circulating concentrations of ACTH and cortisol impair mechanisms responsible for puberty establishment



Effects of Cortisol on Reproduction



- Study by Breen et al. (2005):
- Cortisol infusions in sheep simulating one-third, one-half and maximal plasma cortisol concentrations that would be induced by isolation stress
- Infusions during early and mid-follicular phases

Effects of Cortisol on Reproduction



- Results:
 - Suppression of LH pulse frequency
 - Delays or prevents estradiol peak
 - Delays or blocks LH and FSH surges
- **Use of LAN's in non-domestic** species during assisted reproduction have resulted in easier handling and significantly lower cortisol levels just before oocyte collection

Haloperidol



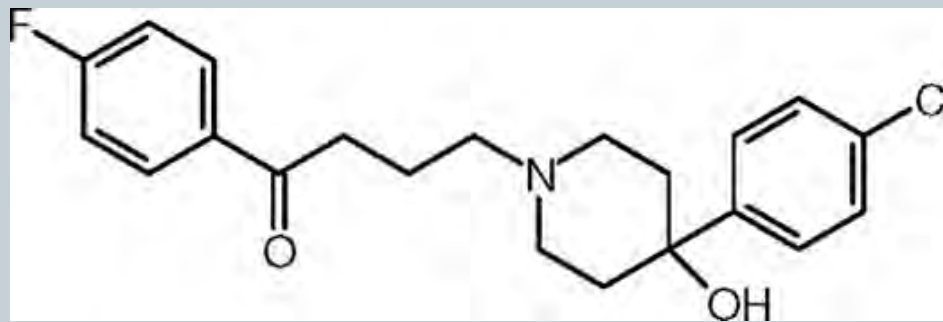
- Antipsychotic and tranquilizing agent
- Long-acting neuroleptic: 10-12 hour duration
- Can be orally administered
- Short and long-term use in wildlife
 - ✦ Bongo Antelope – 1 mg/kg PO SID
 - ✦ Mongolian Wild Horse – 0.3 mg/kg PO SID
 - ✦ Elephants – 40-100 mg PO BID
 - ✦ Recommended for GOHR – 0.05- 0.1 mg/kg PO with max 16 hr duration



Haloperidol



- Does not cause hypothermia or hypotension
 - ✦ Side effects: extra-pyramidal side effects have been seen (especially when further stressed with hyperthermia, noise and excitement during transportation) – rare and transient
- Studies have shown that haloperidol administration is associated with an increase in prolactin secretion - however, we did not anticipate this would negatively impact Indian rhino estrous cycles



Pharmacokinetics



- Bongo Antelope
 - ✦ Peak behavioral effects 2 hr post dose, peak serum 10 hr post dose
 - ✦ Haloperidol absorbed gradually and reliably from the GI tract even in the presence of food
- Sprague-Dawley rats
 - ✦ Significant amount of haloperidol radioactivity in urine within 8 hours of administration
 - ✦ Clear GI tract by 72 hours
- Humans
 - ✦ Mean elimination $t_{1/2}$: 17.9 ± 6.4 hr
 - ✦ Time lag before absorption: 0.82 ± 0.25 hr
 - ✦ Bioavailability: 0.65 ± 0.14
 - ✦ Extensive tissue distribution

Objectives



- Use Haloperidol to alleviate the negative physiological effects of temperament on:
 - Reproduction
 - Exhibit behavior
- Compare urinary cortisol concentrations
 - Urine was collected in morning
 - Diurnal variations



Objectives



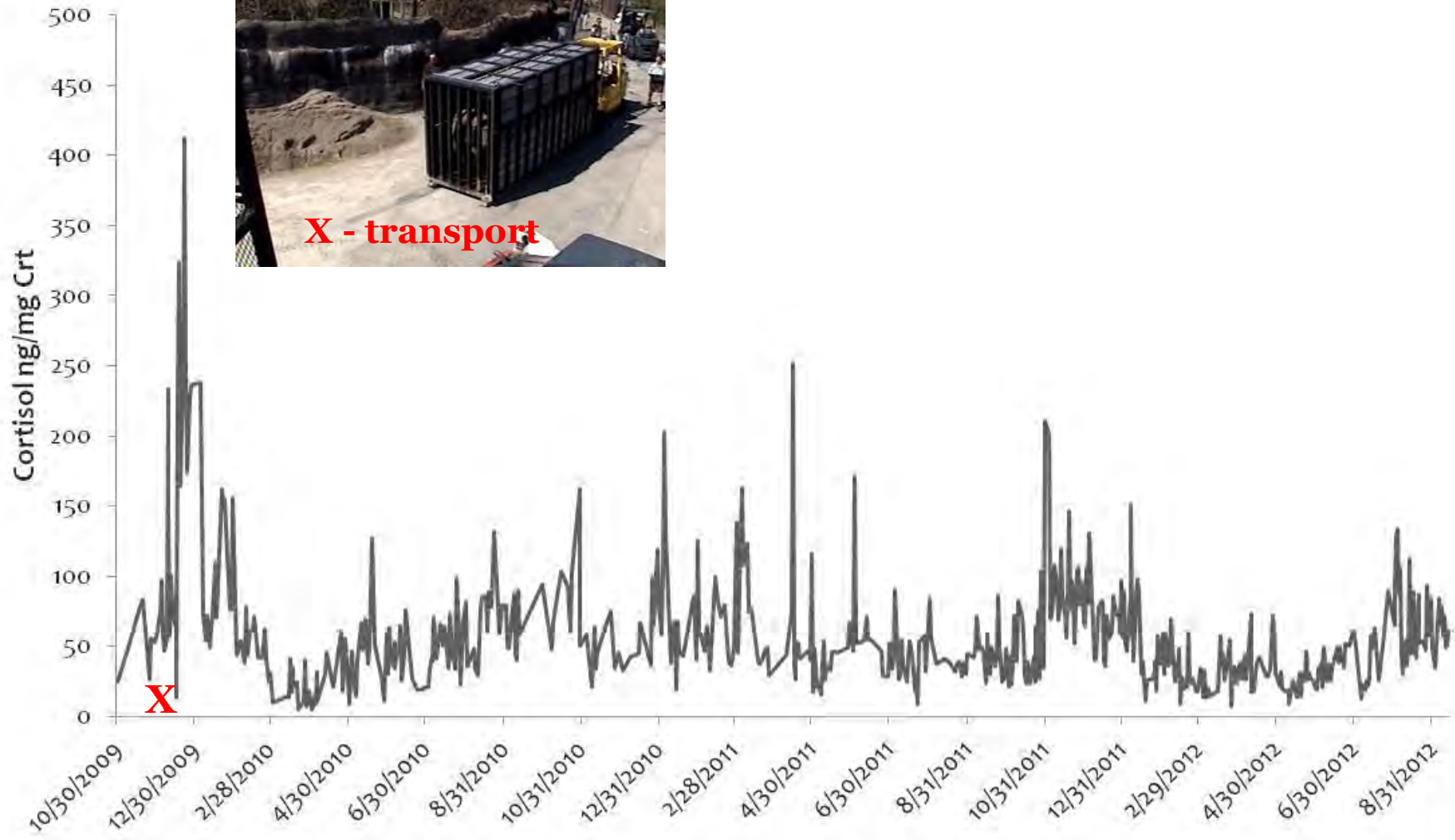
- Compare behavioral correlates related to public exhibition and handling for reproductive assessment (ultrasonography)
- Haloperidol assay and validation
 - Commercially available enzyme-linked immunoassay (Neogen, Lexington, KY)
- Haloperidol pharmacokinetics and pharmacodynamics

Haloperidol Dosing

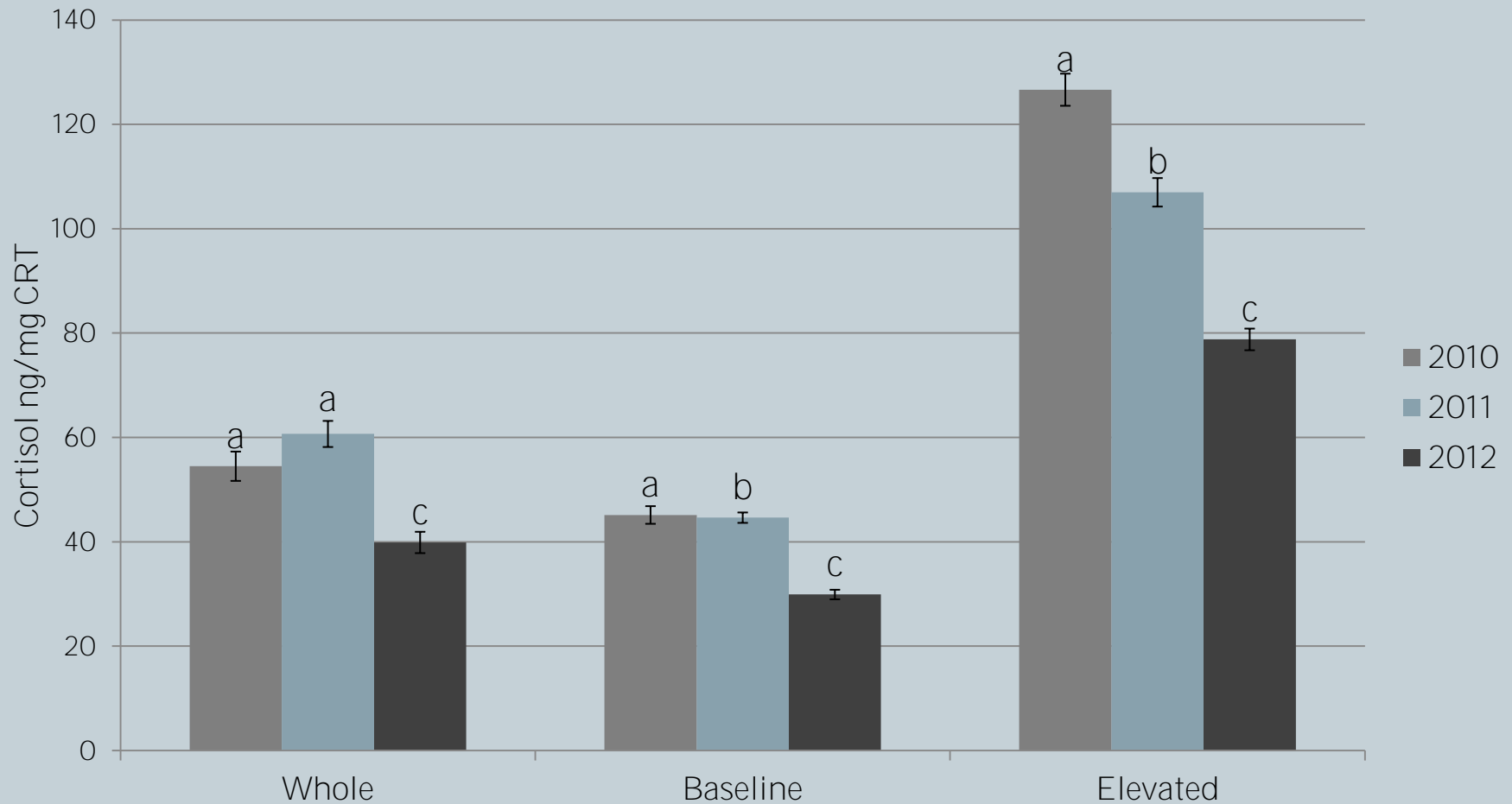


- Oral doses of multiple 10 mg tablets
 - Concealed in a banana and hand-fed to rhino every morning
 - Effect during peak exhibit times
- Estimated weight of the rhinoceros was 1360kg (3000lbs) with dosage of 0.038mg/kg haloperidol
- Received 50mg (0.037mg/kg) once daily for the first 50 days of treatment
- Dosage increased to 80 mg (0.058mg/kg) once daily for 153 days
- Dose was tapered for the last 34 days to discontinue treatment
- Another female Indian rhinoceros housed at the Cincinnati Zoo did not receive haloperidol treatment
 - Control for background urinary haloperidol concentrations

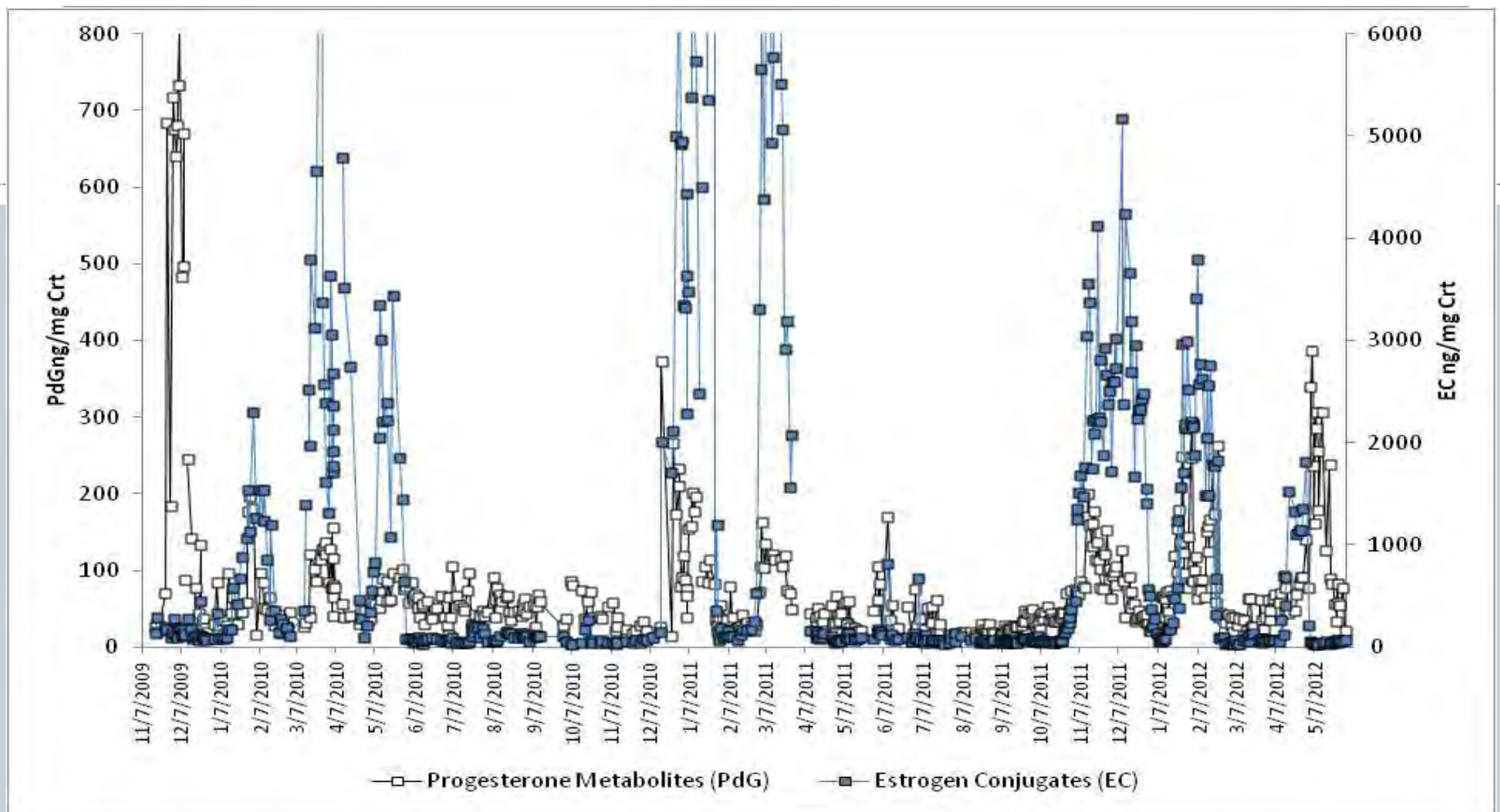
Urinary Cortisol



Urinary Cortisol Comparisons

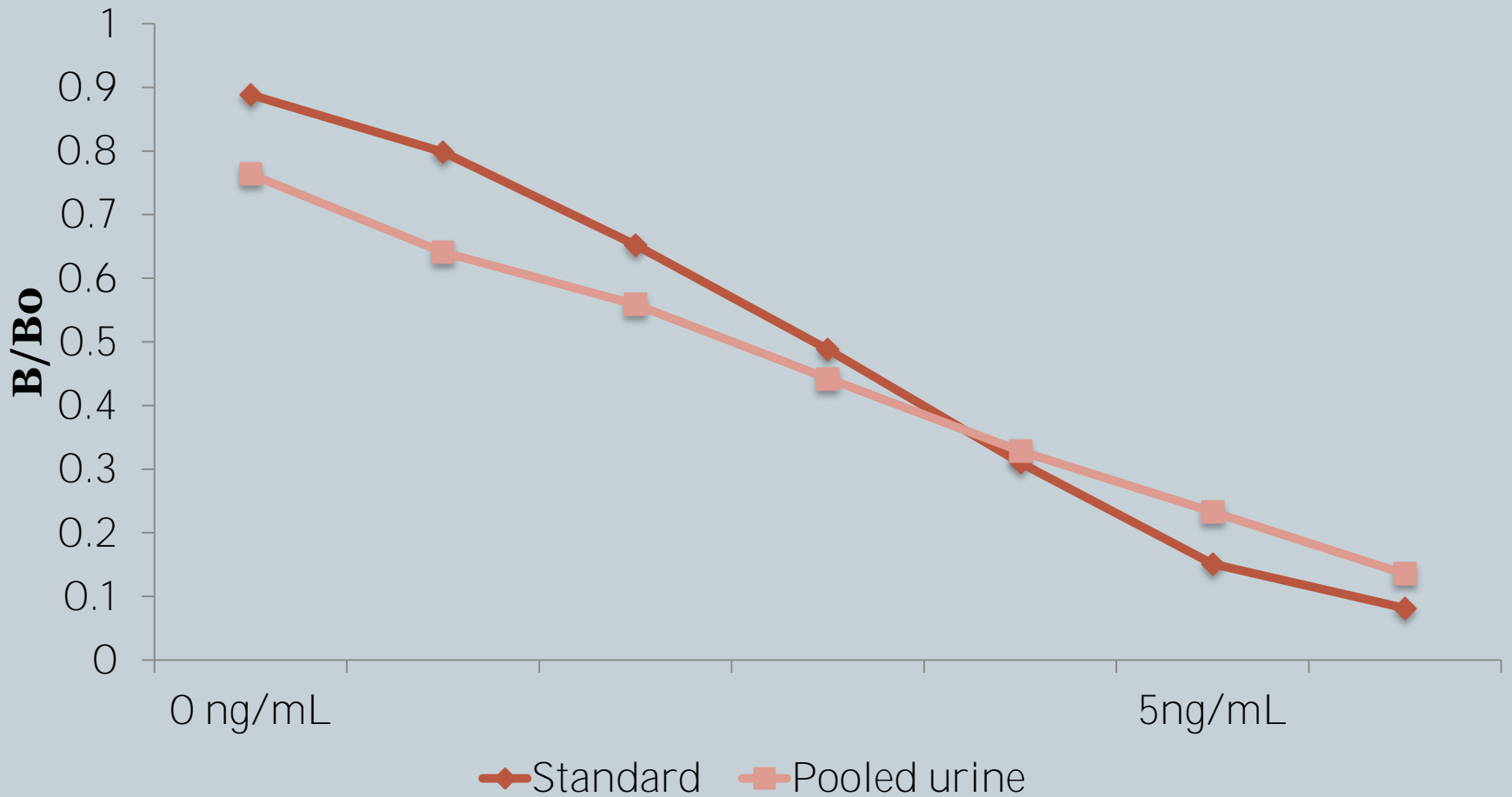


*different superscripts indicate statistical significance $P < 0.05$ within each category (whole, baseline, elevated)

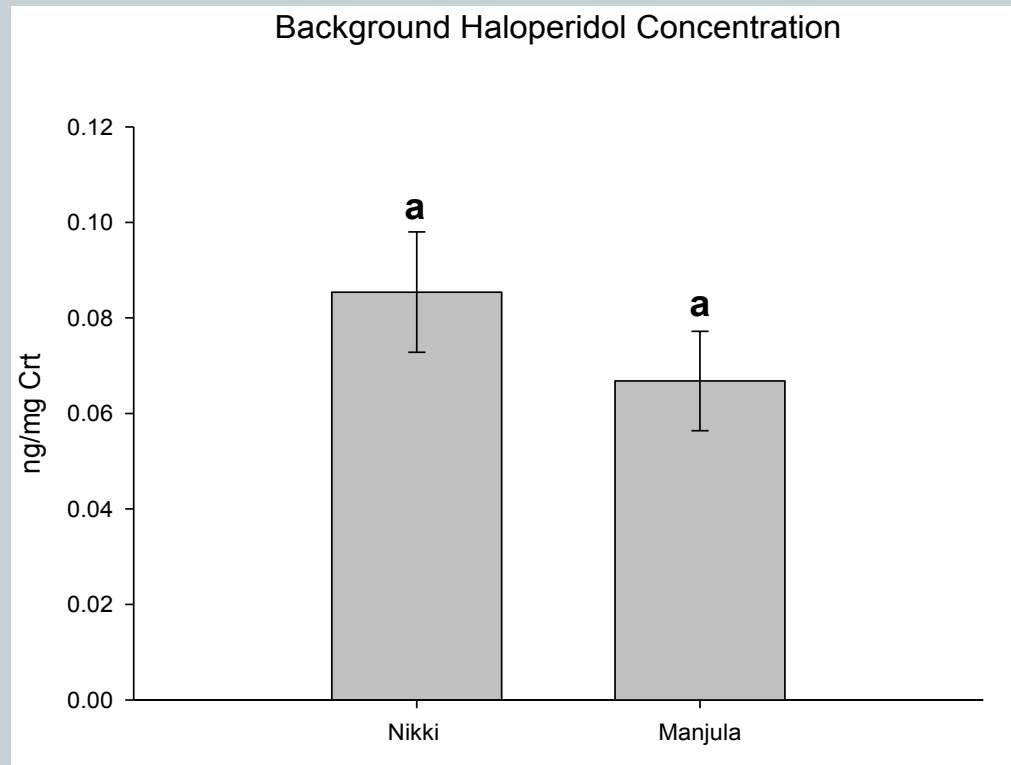


- Positive correlation between EC and cortisol:
 - Urinary EC and cortisol Correlation Coefficient = 0.163 (P <0.05)
- Not exhibiting normal estrous cycles
- Lack of cycles during time of year when out on exhibit
- First normal ovulatory cycle April 2012
- Otherwise, cystic follicles associated with long follicular phase >14 days

Haloperidol Assay Validation

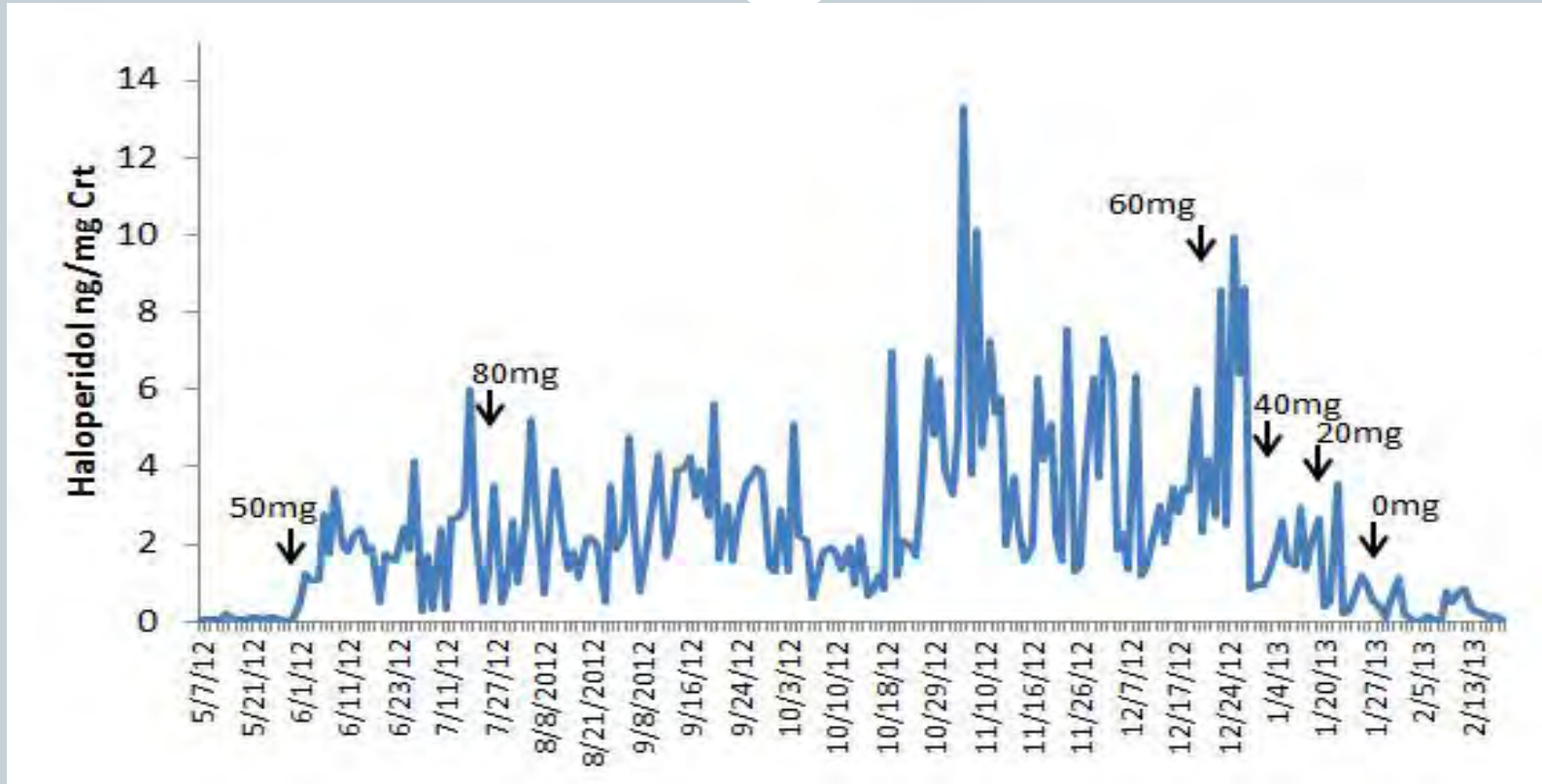


Background Concentrations



There were no differences ($P=0.16$) in background concentrations (0.76 ± 0.01 ng/mg Crt; 0.13 ± 0.01 ng/mL) of haloperidol between Indian rhinos, and both were similar to background values reported in equine urine (<0.18 ng/mL).

Dose-dependent Excretion



A dose dependent excretion effect was observed during dosage decline and concentrations returned to background levels within 2 weeks of treatment ending.

Zoo Volunteer Watch



- 2 hour period: 10am – 12pm daily
- 10 day baseline behavior and exhibit use
- Nikki: 6 day baseline behavior data for comparison of exhibit use and activity (control)
- Change of plan in study design – Manjula off exhibit for 21 days due to need to modify exhibit posts/hot wire



Ethogram for Indian Rhino Manjula

10:00 AM to 12:00 PM on ____ / ____ / 2012

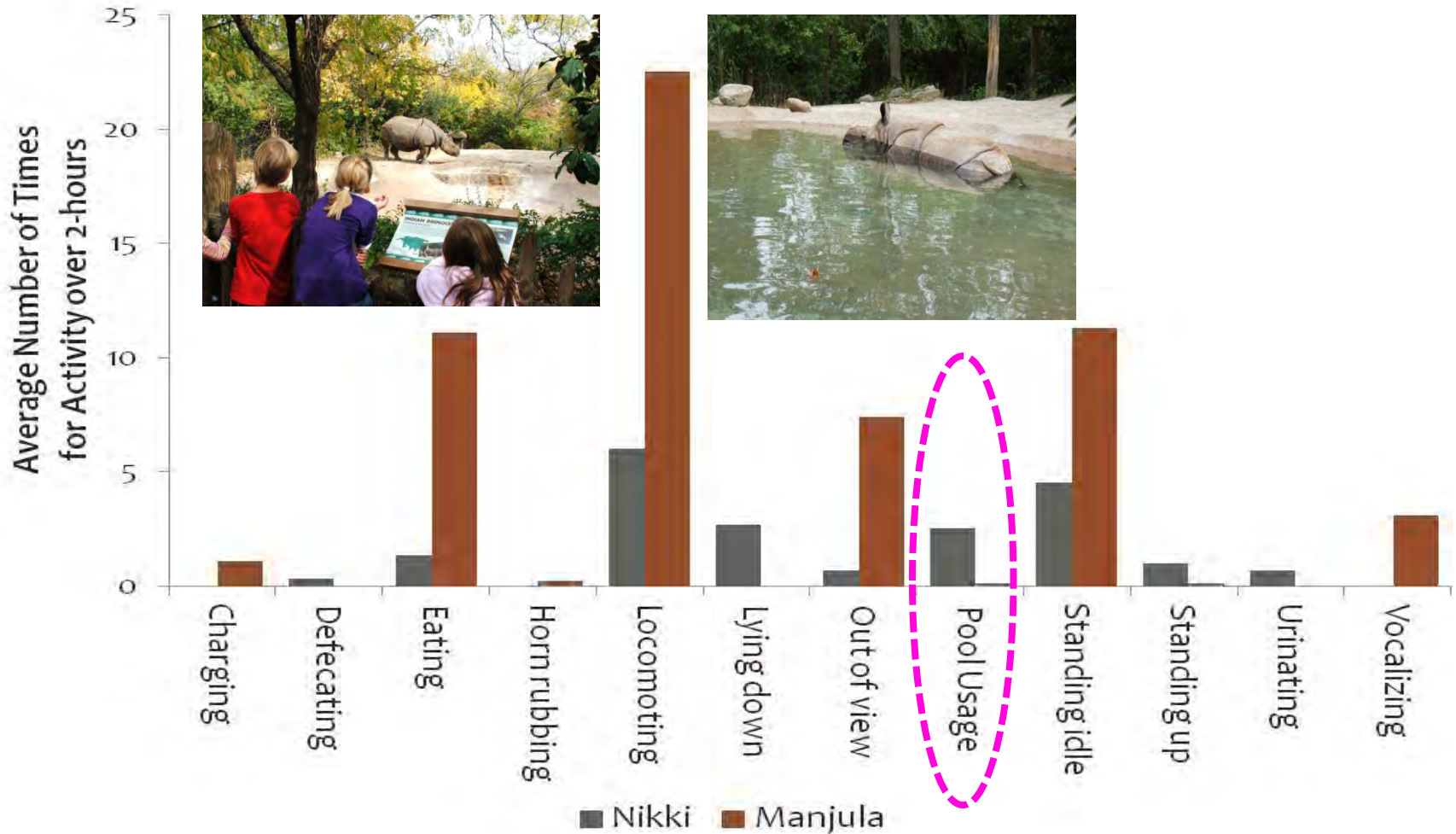
Activity/Time	10:00	10:30	11:00	11:30	12:00
Charging					
Defecating					
Drinking					
Eating					
Hind leg locking					
Horn rubbing					
Locomoting					
Lying down-lateral					
Lying down-sternal					
Out of view					
Pacing					
Resting					
Playing with toys					
Rubbing					
Standing idle					
Standing up					
Straining					
Urinating					
Urine spraying					
Vocalization					

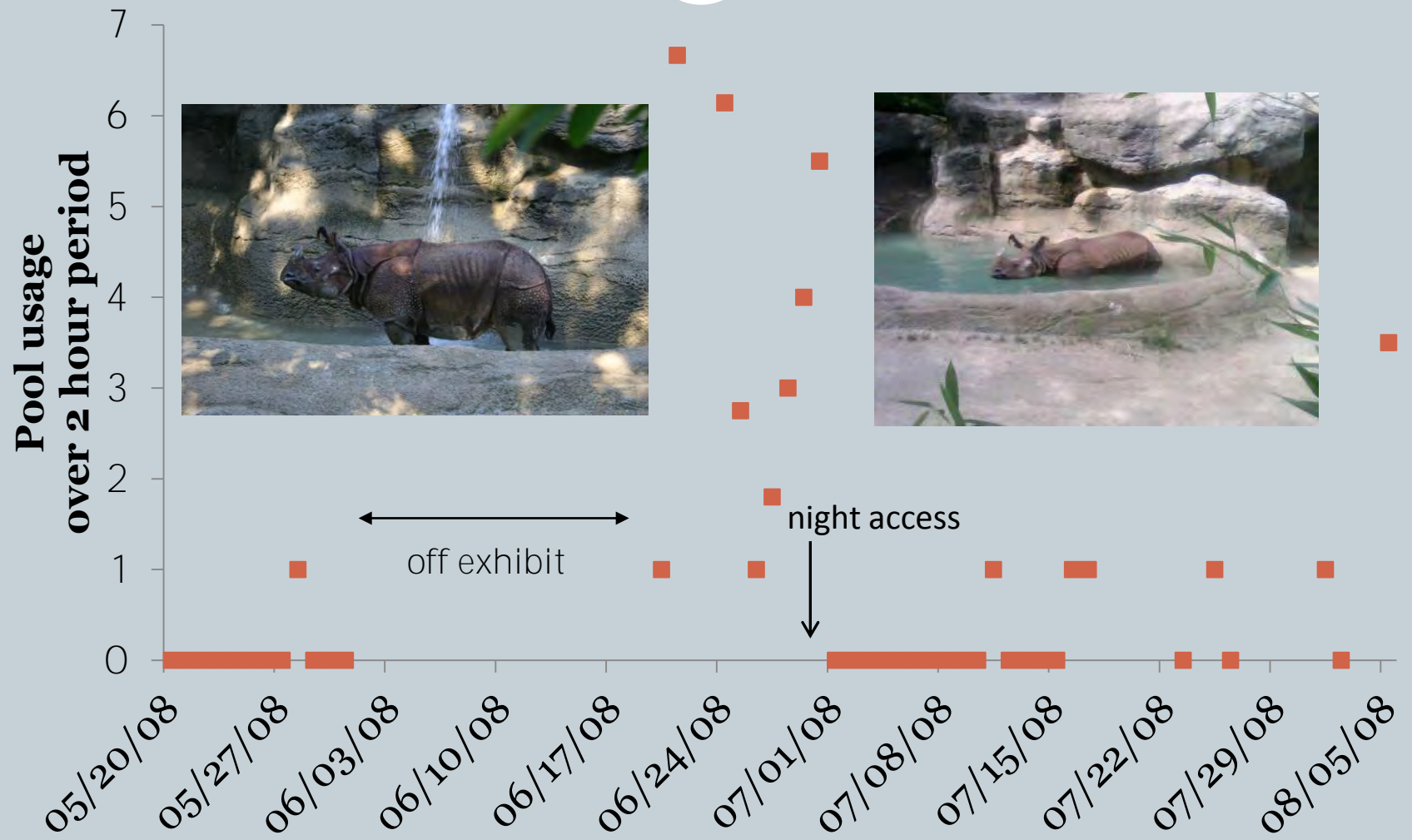
Comments

Observer initials:

Reviewer notes:

Activity levels





Conclusions



- This is the first data with regard to urinary pharmacokinetics/pharmacodynamics of the LAN haloperidol in the Indian rhinoceros
- No extrapyramidal side effects during 240 days of treatment



Conclusions



- Haloperidol may be useful in:
 - Improving welfare of Indian rhinos or other animals exhibiting difficulty adjusting to new exhibits
- Haloperidol did not appear to interfere with estrous cycle and ovulation



Acknowledgements



- Procter and Gamble Pet Care
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- Pat Hermes

Questions?

