#1805 JET-BP in Socially Housed Nonhuman Primates: Comparison of Covance Sites and Study Considerations

L.M. Kreckler[1], J. Grosh[1], J. Schneider[1], M. Niehoff[2], C.M. Foley[1] and M.A. Osinski[1]
[1]Covance Laboratories Inc., Madison, WI; [2]Covance Laboratories GmbH, Münster, Germany

Abstract

Nonhuman primates (NHPs) are a social species and benefit from group housing. Positive social interactions can lead to lower stress which is important for animal welfare, but also for reducing potential confounding effects in a toxicology study, especially for sensitive cardiovascular end points. The European Council requires that NHPs be housed with one or more cohabitants, while US policy strongly recommends doing so. While social housing is highly desirable for enhancing animal welfare, it can introduce challenges to the collection of high quality cardiovascular data via jacketed external telemetry with blood pressure (JET-BP). A comparison of two Covance sites was undertaken to evaluate the consistency of JET-BP assessments in ETS 123 compliant pens across sites. At both Covance-Madison and Münster, etilefrine was administered to NHPs at 0, 1, or 10 mg/kg on 3 occasions to 12 animals (4/group) and cardiovascular changes assessed using JET-BP technology. Systolic blood pressure was slightly increased at 1 mg/kg (10 mmHg; Münster) and markedly increased at 10 mg/kg (≥25 mmHg; Madison and Münster). In addition to comparable results between two Covance sites, we demonstrated a slight reduction in systolic, diastolic and mean arterial pressure and heart rate in NHPs in pen versus individual housing (Madison). Finally, we showed reliable longevity of the blood pressure assessment with 33/36 animals (94%) maintaining consistent signals through 6 months. While we have shown benefits to hemodynamics and consistency between test sites, implementation of JET-BP in group housing does impact study design. Importantly, staggered initiations are required which can have a profound effect on scheduling of other study events and study duration which impacts cost and project timelines. Parallel dosing designs are inherently less sensitive than crossover designs. Therefore, careful consideration of the requirements and limitations of JET-BP in a group setting is recommended to ensure best practice.

Methods

- Cynomolgus monkeys (NHPs) were implanted with a blood pressure transmitter at two Covance locations (Madison, WI and Münster, Germany) and were housed in European guideline (ETS123) compliant pens. NHPs were given etilefrine (non-specific adrenergic agonist) at 1 and 10 mg/kg and sotalol (non-selective β-blocker and hERG channel blocker) at 30 mg/kg by oral gavage.
- JET-BP collections were completed on days of dosing for at least 90 minutes prior to dosing and continuously for at least 20 hours postdose.
- Data collected were used to determine PR, QRS, QT and rate-corrected QT (QTc); systolic, diastolic and mean arterial pressures; heart rate; and arterial pulse pressure. Data were summarized as one-hour (light phase) or two-hour (dark phase) averages.

Cardiovascular Data Consistency Across Two Covance Sites

Etilefrine

- Etilefrine given on three occasions at 1 and 10 mg/kg (data not shown at 1 mg/kg) significantly increased systolic pressure (Figure 1A) and pulse pressure (Figure 1B), to comparable levels when assessed by JET-BP at Covance-Madison or Covance-Münster.

Sotalol

- Sotalol given at 30 mg/kg significantly increased QT interval (Figure 1C) and decreased heart rate (Figure 1D) to comparable levels when assessed by JET-BP at Covance-Madison or Covance-Münster.

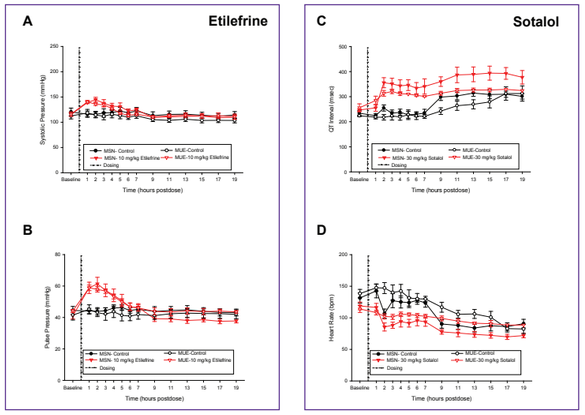


Figure 1. Representative JET-BP data from two Covance sites (Madison [MSN] and Münster [MUE]) for systolic pressure (A) and arterial pulse pressure (B) after treatment with 10 mg/kg etilefrine; and for QT interval (C) and heart rate (D) after treatment with 30 mg/kg sotalol; n = 4.

Longevity of BP Device

- Reliable signals from all implants were detected through 9 weeks when the first animal lost BP signal.
- The majority of animals (94%) maintained consistent signals for 6 months. After 6 months, devices began to fail with greater frequency, possibly due to battery failure.

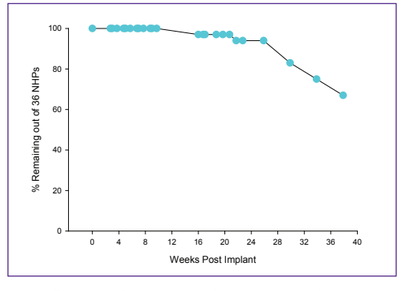


Figure 2. Percentage of viable BP implants remaining post implantation for 36 NHPs.

Comparison of Pen and Individual Housing at Covance-Madison

- Statistical analysis using a paired *t*-test showed that systolic (Figure 3A), diastolic (Figure 3B) and mean arterial (Figure 3C) pressure, as well as heart rate (Figure 3D) were slightly lower in pen housing compared with individual housing (Table 1).

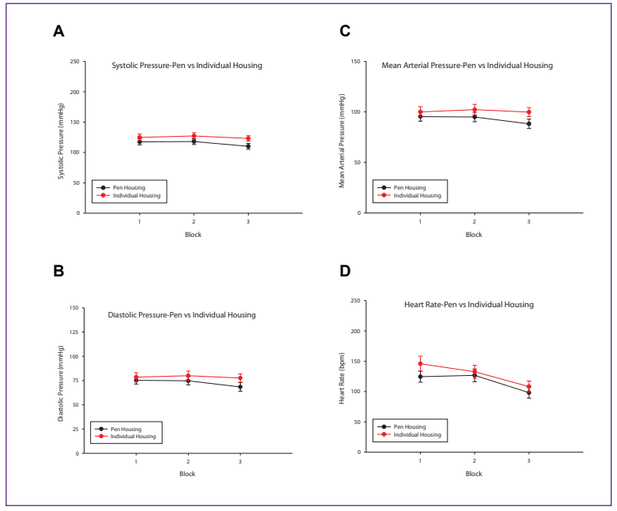


Figure 3. Comparison of hemodynamic parameters in untreated animals in pen and individual housing in Covance-Madison; n = 4. JET-BP data for systolic (A), diastolic (B), mean arterial pressure (C) and heart rate (D). Values represent mean hemodynamic data collected from four control animals during three different collection intervals in each housing condition. Data averaged by block where Block 1 = predose, Block 2 = postdose light phase and Block 3 = postdose dark phase.

Note: Data presented previously at SOT 2014.

Table 1. Comparison of Blood Pressure and Heart Rate in Control Animals in Pen and Individual Housing

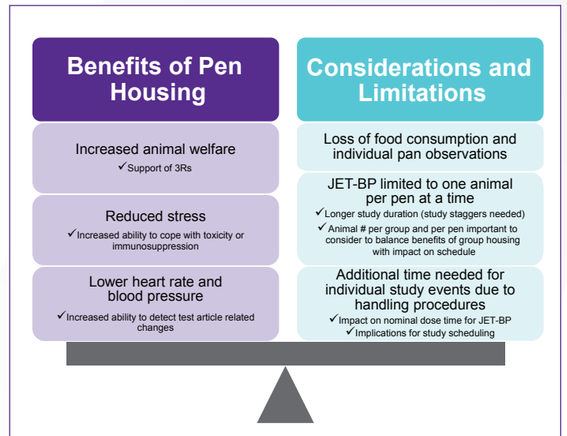
	Mean ± SEM[a]		
	Pen Housing[b]	Individual Housing[b]	Individual Compared to Pen-Difference (%)
Systolic Pressure (mmHg)			
Block 1	117± 5	125± 6	+8 (7%)
Block 2	118± 5	127± 5	+9 (8%)
Block 3	110± 5	123± 5	+13 (12%)
Diastolic Pressure (mmHg)			
Block 1	75 ± 4	79 ± 5	+4 (5%)
Block 2	75 ± 4	80 ± 5	+5 (7%)
Block 3	68 ± 4	78 ± 4	+10 (15%)
Mean Arterial Pressure (mmHg)			
Block 1	95 ± 5	100 ± 5	+5 (5%)
Block 2	95 ± 5	102 ± 5	+7 (7%)
Block 3	88 ± 5	100 ± 4	+12 (14%)
Heart Rate (bpm)			
Block 1	124 ± 9	146 ± 12	+22 (18%)
Block 2	127 ± 10	133 ± 11	+6 (5%)
Block 3	98 ± 9	108 ± 9	+10 (10%)

Block 1 = predose; Block 2 = postdose light cycle; Block 3 = postdose dark cycle
a Values represent mean hemodynamic data collected from 4 control animals (no reference drug) on 3 different collection intervals per housing condition (19 hour collections), averaged by block.
b The same animals were used in both housing conditions. First collections were completed in pen-style housing. Following completion of collections in pen housing, animals were transferred to individual housing, acclimated for 3 weeks, and then next set of collections was completed.

Note: Data presented previously at SOT 2014.

Conclusions

- JET-BP measurements from NHPs at two Covance sites (Madison and Münster) were comparable.
- Good longevity (through 6 months) of the BP device was demonstrated at Covance-Madison.
- Animals in pen housing (group-housed) had slightly lower heart rate and pressure compared with individually housed animals.
- Regulatory agencies already require or recommend social housing of NHPs to enhance animal welfare. However, social housing with JET-BP adds challenges that should be considered during study design to ensure desired study endpoints and program milestones are appropriately met.



Presented at SOT 2015

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