Pair-housed dog telemetry: Animal welfare refinement with early indications of similar study sensitivity

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Introduction

- Dogs are routinely housed individually during telemetry recording sessions. This is required when using the legacy DSI system, as animals need to be separated by at least 1 metre to avoid cross-talk between the signals transmitted on the same frequency. Whilst this does not prevent the inclusion of a companion dog (if pen size allows), in reality this tends to be avoided due to concerns around the behavioural impact of group housing on data values and quality, and potential for bioanalytical cross-contamination.
- Most facilities co-house dogs before studies and between recording sessions within a study, in compatible groups which remain together for many years. Therefore, separation during recording periods may introduce additional and unwanted stress. It is recognised that haemodynamic parameters are improved in dogs housed with their usual run mate, rather than singly-housed[1].
- With a recent upgrade to DSI digital hardware (PhysioTel® Digital) within the Charles River (CRL) Edinburgh facility, as telemetry signals now transmit over different frequencies it is possible to record from multiple animals within the same area. We now record our telemetry data from pair-housed dogs and present our experiences and recommendations.

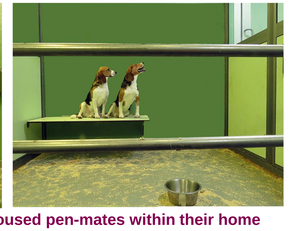

Figure 1a and 1b: Examples of pair-housed pen-mates within their home (recording pen) environment. One TRX-1 transceiver is required per 4.5 m² pen.

References:

1) Klumpp, A., Trautmann, T., Markert, M., & Guth, B (2006). Optimizing the experimental environment for dog telemetry studies. J Pharm Tox Meth 54: 141-149.
2) EU directive 2010/63/EU. On the protection of animals used for scientific purposes.
3) Ewart, L. et al (2013). A multi-site comparison of in vivo safety pharmacology studies conducted to support ICH S7A & B regulatory submissions. J Pharm Tox Meth 68: 30-43.

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Methods

- Male Beagle dogs were surgically prepared with DSI PhysioTel® Digital L21 radio transmitters for measurement of arterial blood pressure, left ventricular pressure parameters, lead II ECG and body temperature.
- Dogs were housed in groups of 2 in floor-pens meeting the requirements of the EU guidelines[2] (at least 4.5 m²). These pairs remained housed together for the entire study period.
- Two dosing regimes were employed, as below. Test item and control were administered at dose intervals of 3 to 7 days and recordings were made from approximately 1 hour pre-dose to between 24 and 96 hours post-dose (according to the pharmacokinetics of individual compounds).

Animal ID	Pen	Test item dose level (mg/kg)			
		Day 1	Day 5	Day 8	Day 12
1	1	Control	Low	High	Mid
2	2	Low	Mid	Control	High
3	3	Mid	High	Low	Control
4	4	High	Control	Mid	Low

Table 1: Williams' latin-square design. Only one dog within the pen is dosed, the other acts solely as a companion.

Animal ID	Pen	Test item dose level (mg/kg)			
		Day 1	Day 5	Day 8	Day 12
1	1	Control	Low	Mid	High
2	1	Control	Low	Mid	High
3	2	High	Mid	Low	Control
4	2	High	Mid	Low	Control

Table 2: Partial latin-square design. Both dogs within the pen receive the same dose level to reduce the potential for bioanalytical cross-contamination.

Pre-dose baseline data (single vs pair-housed)

	CRL Single-housed (n=48)	CRL Pair-housed (n=28)
Systolic Blood Pressure (mmHg)	154 ± 1.6	168 ± 2.9
Diastolic Blood Pressure (mmHg)	88 ± 0.9	95 ± 1.4
Mean Blood Pressure (mmHg)	111 ± 1.1	122 ± 2.0
Heart Rate (bpm)	79 ± 2.6	97 ± 3.8
PR Interval (ms)	93 ± 1.6	89 ± 1.9
QRS Duration (ms)	43 ± 1.3	37 ± 0.5
QT Interval (ms)	232 ± 2.3	226 ± 3.2
QTcR (ms)	233 ± 1.9	231 ± 1.7
Body Temperature (˚C)	37.4 ± 0.1	37.3 ± 0.1
dP/dt+ (mmHg/s)	3864 ± 162	4720 ± 158.6
dP/dt- (mmHg/s)	3761 ± 93.5	3957 ± 113.2
Systolic Left Ventricular Pressure (mmHg)	127 ± 1.5	132 ± 3.8
QA Interval (ms)	120 ± 1.4	119 ± 1.5

Table 3: Mean ± sem of individual dogs at baseline on vehicle dosing session from 12 studies where dogs were single-housed (=48 individual dogs) or from 7 studies where dogs were pair-housed (=28 individual dogs). Values are generally similar between the two housing conditions. Some indications of higher heart rates are apparent in pair-housed dogs.

Results

Example study 1 (William's latin-square)

As this compound was known to have an extended pharmacokinetic profile, the telemetry study was designed to record for 4 days continuously (single dose, at 7 day intervals). UK regulations do not allow dogs to be separated for this length of time, so the dosed dog was joined by an un-dosed companion.

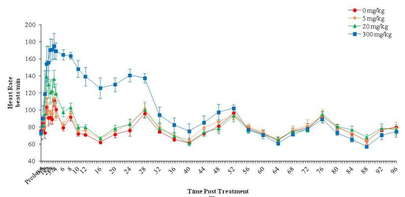

Figure 2a: Heart rate (group mean ± sem, n=4 dogs)

Note pre-dose heart rates of ~75-90 bpm in these pair-housed dogs.

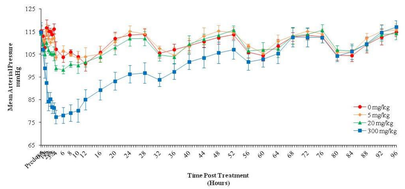

Figure 2b: Mean arterial blood pressure (group mean ± sem, n=4 dogs)

Comparison of detectable differences – sensitivity of the different study designs

Parameter	Williams' latin-square Single-housed	Williams' latin-square Pair-housed Un-dosed companion	Partial latin-square Pair-housed Dosed companion	Ascending design Single-housed
Number of studies used in analysis	4	1	4	3
Systolic Blood Pressure	14	10	13	12
Diastolic Blood Pressure	17	11	14	17
Mean Blood Pressure	15	9	13	14
Heart Rate	33	36	33	34
PR Interval	12	10	10	16
QRS Duration	9	5	4	9
QT Interval	9	8	10	11
QTcR	6	4	6	8
QA Interval	8	7	7	15
dP/dt+	31	27	38	29
dP/dt-	22	21	24	24
Left Ventricular Systolic Pressure	16	16	16	17
Body Temperature	3	2	3	3

Table 4: Effect size (as % of vehicle control) detected with 80% power, using n=4 dogs.

Data from pair-housed dogs (either with un-dosed or dosed companion) has similar study sensitivity as the industry standard practice (latin-square design, single-housed dogs). Additionally, the study sensitivity is improved over previous study designs (ascending dose design, single-housed dogs[3]).

Results

Example study 2 (vehicle and atenolol, single vs pair-housed)

We tested a reference item (atenolol, 3 mg/kg oral gavage administration) in 4 dogs housed individually and in 4 dogs housed with a companion.

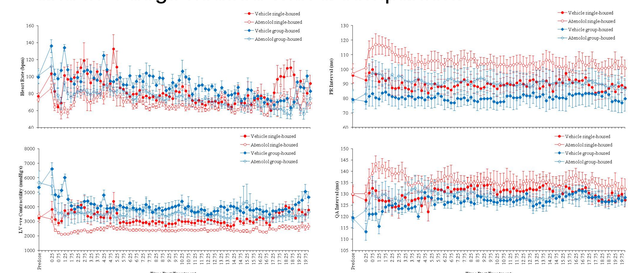

Figure 3a (Heart Rate), b (PR Interval), c (LV dP/dt+) and d (QA Interval)
Group mean ± sem (n=4 dogs). In this study, pair-housed dogs have higher heart rates than single-housed dogs, with concomitant lengthening of PR intervals.

Conclusions

- Cardiovascular data can be obtained from pair-housed dogs with a similar sensitivity to data obtained from single-housed dogs. Reference item effects can be detected using this design, in a similar manner as for single-housed dogs.
- Some of the apparent differences observed between these conditions could be due to other confounding factors (e.g., different animal facility, dose routes and different dogs – ages or time in colony / number of studies used on).
- This is a '3Rs' refinement: dogs receive companionship as there is no need for separation during recordings (reducing potential stress).
- This refinement can be used with any supplier hardware, assuming pen sizes are sufficient for co-housing, using either an un-dosed companion or a dosed companion. However, the latter option maximises room occupancy, study throughput, wash-out periods between studies and stock colony sizes and is our proposed way of working.
- This refinement can be adopted with confidence and can also be applied to external telemetry recordings within toxicology studies.

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