

ASSESSMENT OF DRUG-INDUCED CARDIOVASCULAR EFFECTS BY TELEMETRY IN GROUP-HOUSED CYNOMOLGUS MONKEYS

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INTRODUCTION

New Non-Human Primate (NHP) telemetry facilities have been designed at Biotrial for group-housing in large modules. The purpose was to promote social interaction, ensure animal welfare and implement the 3Rs rule, as stipulated in the new European Directive on the protection of animals used for scientific purposes (2010/63/EU). Safety assessment of cardiovascular function in non-human primates (NHP) has been performed for many years using telemetry. In order to avoid restraining the animals and to allow them to remain in their large home cage, we implemented the recently updated telemetry hardware (DSI™ PhysioTel Digital), with multifrequency and long transmission range, which allows telemetry recording in animals group-housed in large modules. In addition, we introduced operant conditioning procedures with positive reinforcement to achieve active participation of the animals and thereby decrease stress during experiments. Finally, high definition video monitoring is used to evaluate drug effects on animal behaviour, thus avoiding artefacts created by the presence of the experimenter in the telemetry room. The aim of the present study was to validate the telemetry setting in pair-housed NHP, in terms of animal behaviour, quality of blood pressure and ECG signals and cardiovascular responses to moxifloxacin and sotalol which are known to prolong ventricular repolarization in humans.

MATERIALS & METHODS

Animals and Surgery

- > 4 male Cynomolgus monkeys (*Macaca Fascicularis*, origin Mauritius, BIODPRIM, Baziège, France) - 3.5-5 kg.
- > Instrumented with HD-L11 transmitters with Solid Tip ECG Leads.
- > Surgery under Ketamine/Xylazine anaesthesia
- > Per- and post-operative care:
 - > Analgesia: buprenorphine 10µg/kg IM
 - > Antibiotherapy: amoxicilline 30 mg/kg IM
 - > Anti-inflammatory treatment: Finadyne 5 mg/kg SC

Telemetry system: PhysioTel Digital 
(Data Sciences International, St. Paul, MN, USA).

Acquisition and Analysis: HEM software v.4.3 
(Notocord Systems, Croissy Sur Seine, France).

Experimental conditions

> Part 1: Evaluation of the influence of housing conditions on basal hemodynamic parameters

- > Continuous recording of cardiovascular parameters by telemetry over 24-hour period in animals:
 - > Singly or pair-housed.
 - > Housed in large modules (4m³) or smaller cages (2m³).

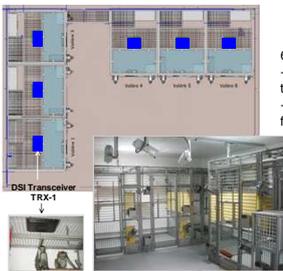


Part 2: Pharmacological validation - effects of Moxifloxacin and Sotalol

- > Moxifloxacin: 30, 90 and 150 mg/kg
- > Sotalol: 3, 10 and 30 mg/kg
- > Vehicle: 0.5% methylcellulose
- > Drugs given orally by gavage (volume: 5 mL/kg)
- > Animals fasted for 12-17h before treatment (food provided ~6h post dosing).
- > **Parameters measured**
 - > Arterial blood pressure (mmHg)
 - > Heart rate (bpm)
 - > ECG intervals (ms): PR, QRS, QT, QTc
 - > Continuous recording of cardiovascular parameters over 24 hours post-dosing.
- > **Statistical analysis**
Two-way ANOVA (Treatment x Time) with repeated measurement on both factors.

RESULTS

Facilities, Housing and animal training



Primate telemetry room with 6 large inter-connecting modules.

- One Transceiver (TRX-1) at the top of each module.
- HD video monitoring system in front of each module.

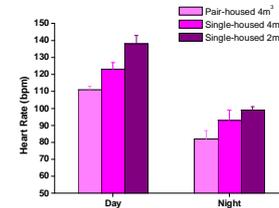


Example of environmental enrichment with suspended mirror.



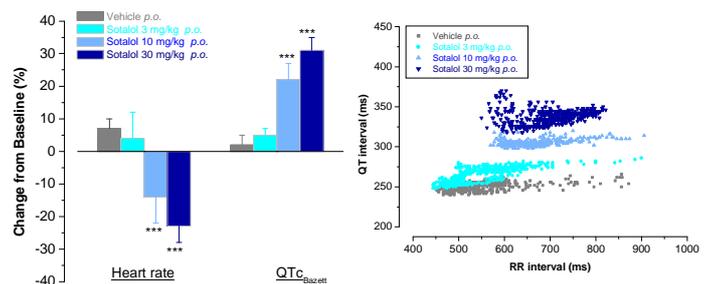
"clicker-training" to the weighing procedure with positive reinforcement.

Influence of environmental conditions



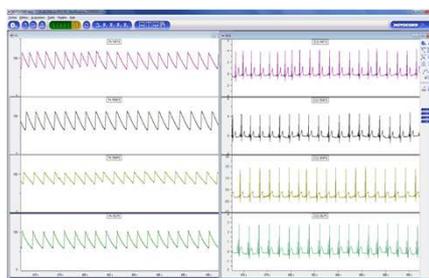
These data demonstrate that changes in housing conditions have an impact on basal hemodynamic parameters, and particularly on heart rate, with increased values in singly-housed animals. This effect is apparent in large modules, and even more so when animals are housed in smaller cages.

Pharmacological validation



Sotalol induced a dose-related decrease in HR and increase in QTcB, with maximum effects between 2 and 3 hours after dosing (left). Example of an individual QT/RR relationship in one monkey (right).

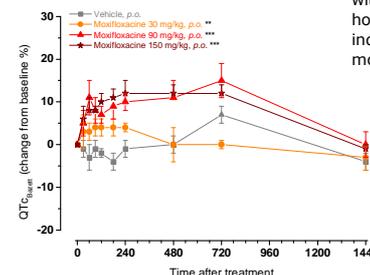
Signals and data



CV Parameters	Baseline values
MAP (mmHg)	90 ± 5
HR (bpm)	103 ± 4
PR interval (ms)	101 ± 4
QRS interval (ms)	39 ± 2
QT interval (ms)	253 ± 9
Body Temperature (°C)	37.8 ± 0.1

High quality arterial blood pressure and ECG signals are obtained in conscious animals pair-housed in large modules.

The housing conditions, combined with the environmental enrichment and animal training, contribute to the baseline values presented.



Moxifloxacin administered at 30, 90 and 150 mg/kg p.o. to conscious monkeys significantly increased QTcBazett.

CONCLUSION

In conclusion, high quality cardiovascular telemetry recording is now possible in non-human primates pair-housed in large cages, therefore complying with the new directive 2010/63/UE. The new housing facilities and experimental conditions (including clicker-training method) result in very low stress, as demonstrated by behavioral observations and baseline haemodynamic parameters. This leads to excellent animal welfare and a strong basis for good science. Furthermore, the cardiovascular effects obtained with two compounds known to prolong ventricular repolarization in humans (moxifloxacin and sotalol) validate these conditions for use in safety pharmacology studies according to ICH S7A and S7B guidelines.