APPLICATION OF A NON-INVASIVE TELEMETRY SYSTEM FOR ELECTROCARDIOGRAM ASSESSMENT IN A DOG TOXICOLOGY STUDY

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INTRODUCTION

A candidate drug entering development, had some concerns regarding cardiovascular liability on chronic dosing. The 1-month, repeat dose dog toxicity study would, therefore, need to address this issue prior to first dose in man. To allow a thorough high quality examination of the electrocardiogram (ECG), a non-invasive, GLP-compliant telemetry system (EMKA Technologies, France) was utilized, to allow a standard toxicology study profile to be maintained, whilst recording ambulatory ECGs.

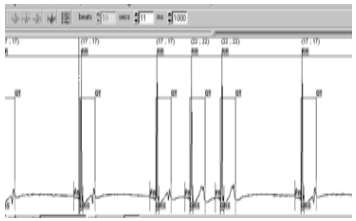
STUDY DESIGN AND METHODS

The study comprised 4 main study groups – vehicle (0 μmol/kg/day), low (45 μmol/kg/day), mid (450 μmol/kg/day) and high (2250 μmol/kg/day) dose. Each group consisted of 3M/3F Alderley Park beagle dogs of at least 10 months old, weighing 8 to 12 kg. ECGs were recorded pre-study, days 2 and 28. In the 3 weeks prior to the first recording session, dogs were acclimatised to wearing the telemetry jackets (Datesand™, UK) and collars (Lomir™, UK) by gradually increasing the duration of exposure from 30 minutes to 8 hours. Surface electrodes (3M™, UK) were applied to consistent anatomical positions (Figure 3), then connected to a transmitter carried in the jacket. Reproducible electrode repositioning was ensured by shaving and marking the sites with permanent ink. The dogs were placed in jackets and returned to their individual pens (4.5 m2) and recording started from 30 minutes pre-dose to 22 hour post-dose. Single lead ECG signal was continuously recorded at a sampling rate of 500Hz. Data was analysed (EMKA ver. 1.5.7) every 5 minutes and heart rate, QRS, PR and QT durations derived at set time-points. QT interval was corrected using Van de Water's Correction formula (1).

RESULTS

An example ECG recording from one dog is shown in Figure 1.

Figure 1. Example ECG recording



RESULTS

Figures 2, 3, 4, 5 and 6 show the pre-study, Day 2 and Day 28 vehicle and high dose heart rate (HR), PR, QRS, QT and QTcV durations (mean ± s.e.m). Daily QT vs. RR regression plots are shown in Figures 7, * and 9.

Figure 2. Heart rate

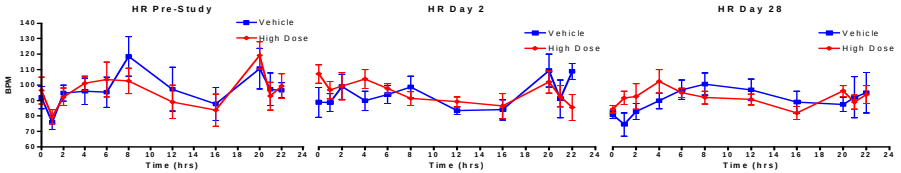


Figure 3. PR interval

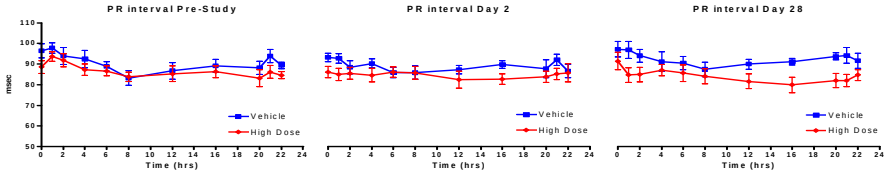


Figure 4. QRS duration

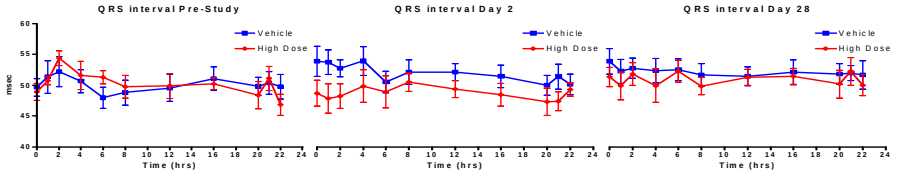


Figure 5. QT interval

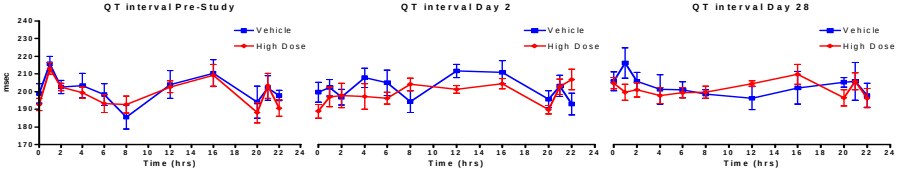
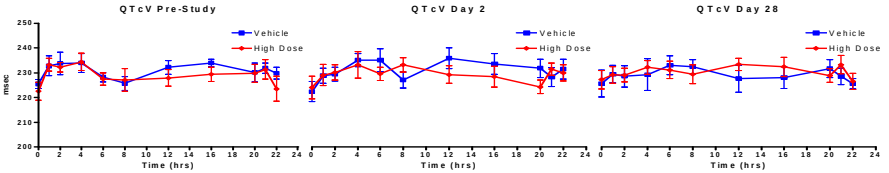


Figure 6. QTcV interval



RESULTS

Total loss of data due to signal drop-out was 3.58% of the total recorded.

No effects on ECG parameters (heart rate, PR, QRS, QT and QTcV intervals) were observed in the compound treated animals when compared to vehicle, after 2 and 28 days of dosing.

Figure 7. Pre-study

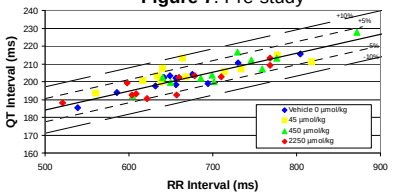


Figure 8. Day 2

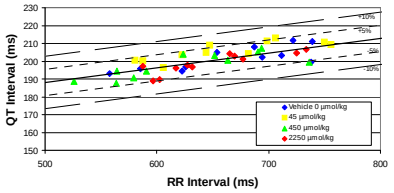
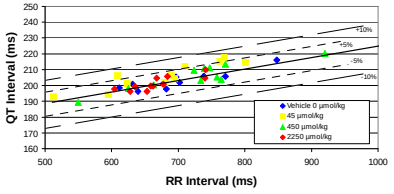


Figure 9. Day 28



CONCLUSIONS

Application of non-invasive telemetry system in a 1-month dog toxicology study enabled a high quality temporal ECG assessment with the definition of no observed effect level for ECG parameters. Therefore, non-invasive telemetry is an appropriate method for ECG assessment on regulatory toxicity studies in dogs.

REFERENCE

1) Van de Water *et al.*, (1989). *J Pharmacol Meth* **22:** 207-217.

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