USE OF A NON-INVASIVE TELEMETRY SYSTEM (EMKA) FOR FUNCTIONAL CARDIOVASCULAR ENDPOINTS IN TOXICOLOGY STUDIES

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Introduction

Historically, physiological monitoring on canine toxicity studies has been limited to recording a conventional electrocardiogram (ECG) on a standing or recumbent animal, usually requiring some restraint or intensive habituation Measurements, therefore, are restricted by practical limitations to relatively stressful "snap-shot" recordings (aimed at Cmax.), leaving long periods when changes in physiological parameters and transient cardiotoxicity could go undetected. To address this issue for a specific compound, an external telemetry system (supplied by EMKA Technologies, France) was tested, purchased and validated and then used to record a single lead EGG for up to 22 hours post-dose on specific days on a one month toxicity study. Providing this additional information as part of this study design (which had suspected QT prolongation effects identified in earlier Safety Pharmacology studies) removed the need for a separate follow-up, invasive one month telemetry study as part of the Safety Pharmacology package.

Study Design & Methodology

3M/3F per group (table 1) had telemetry ECG's recorded pre-study, days 2, 7, 14, 21 and 27 and TK samples on days 1, 8 and 28. Prior to the first recording session, the animals were acclimatised to wearing the telemetry jackets and collars by gradually increasing the duration of exposure i.e. 1, 2, 4, 8 hours to allow acceptance. The electrode sites were also shaved during this acclimatisation period, to save time and reduce the stress to animals during the recording days and the sites marked with a marker pen, if required, to assist the positioning. The sites were swabbed with alcohol and 3M Red Dot ™ Ag/AgCl pre-gelled electrodes gently pressed on to hemithorax to record transversely across the chest. The ECG leads were attached to the electrodes and held in place with self adhesive 3M Vetrap™ or 3M Micropore™ surgical tape, or both, as necessary. The animals were then placed in jackets and returned to their individual pens and recording started (Pictures 1 and 2).

Picture 1: EMKA Transmitter in Jacket

Picture 2: Jacket Held in Position with Velcro Straps

Entry to the animal unit was restricted on recording days to scheduled observations and husbandry procedures. The subsequent data was analysed every 5 minutes over the recording period and then at set time-points post-dose . QT Interval was corrected using Van de Water's Correction formula.

Table 1: Groups and Dose levels

Group	µmol/kg/day	mg/kg/day
1	0	0
2	23.8	10
3	71.4	30
4	143	60
5	214	90

Results

Reproducibility of Vehicle QT Interval data

To demonstrate the reproducibility of the QT measurements produced by the EMKA analysis system (ECGAuto) a regression plot of QT interval against RR for each of the recording days was produced for Group 1 (control) mean data (Figure 1). The data over the normal physiological ranges observed in telemetry animals was consistent over the 27 days.

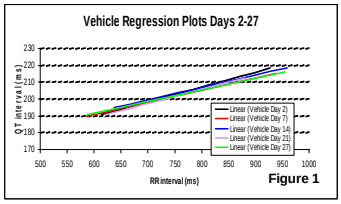


Figure 1

Group 2 (23.8 µmol/kg/day)

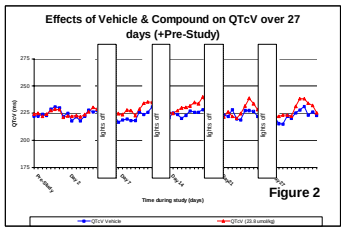


Figure 2

Group 3 (71.4 µmol/kg/day)

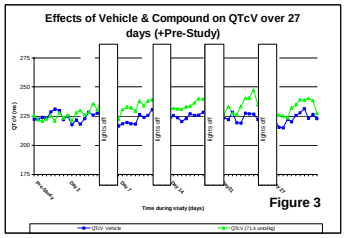


Figure 3

Group 4 (143 µmol/kg/day)

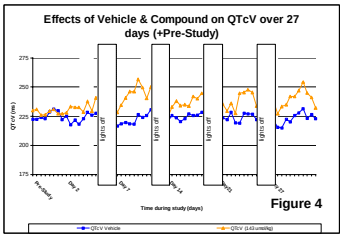


Figure 4

Group 5 (214 µmol/kg/day)

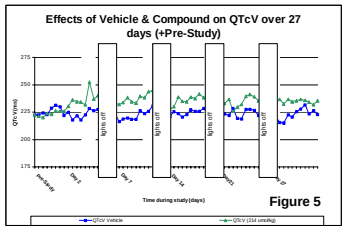
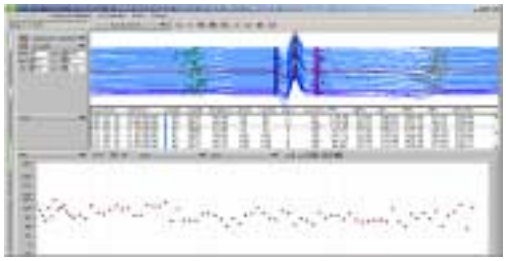


Figure 5

Example of a Trend Graph EMKA Analysis Software Produces



Conclusion

- 143 µmol/kg/day - 60 mg (**Group 4, Fig. 4**): mean 20-25 ms increase in QT_{CV} from Day 7, did not increase further by Day 27.
- 214 µmol/kg/day - 90 mg (**Group 5, Fig 5**): mean 15-20 ms increase in QT_{CV} from Day 2, did not increase further by Day 27. High incidence of emesis in the high dose group.
- 71.4 µmol/kg/day - 30 mg (**Group 3, Fig. 3**): mean 10 ms increase in QT_{CV} from Day 7, did not increase further by Day 27.
- 23.8 µmol/kg/day - 10 mg (**Group 2, Fig. 2**): mean 5 ms increase in QT_{CV} from Day 7, did not increase further by Day 27.

Advantages of non-invasive telemetry

- Continuous ECG monitoring for up to 72 hours
- Non-invasive: less stress full & more 3Rs friendly
- Relatively cheap after initial outlay (re-useable transmitters)
- Technically simple
- User-friendly software (+ GLP and ER/ES compliant)
- Extensive analysis available (trend and stats analysis)
- Measurements appear to be accurate, making the data reliable

and Disadvantages….

- Excessive data, but at least automated analysis takes similar time to normal large toxicity study with hand-measurements
- No Blood Pressure
- Only single lead (6 lead available?)
- Additional resource (1) required in-life (for jacketing dogs and working computers)
- Over interpretation (spontaneous arrhythmias) will need consideration
- Suitable pen size (double pens required for singly housed dogs in AZUK for this length of time)

Proposals for future use…

If the history of a research project is known, and heart rate or ECG effects are suspected, then single dose dog telemetry could run before the dog maximum tolerated dose (MTD) study, if possible.

If this highlights concerns, EMKA telemetry should be included on the repeat phase of the dog MTD to elucidate effects over a short repeat period (MTD; n=4 at same dose level).

If concerns are apparent prior to one month toxicity study, it could be used to elucidate effects over a longer repeat period.

With sensible planning and the coordination of safety pharmacology and dog toxicology studies, quality ECG data can be recorded using an external telemetry system (EMKA) from toxicity studies, sometimes avoiding the need for further, or repeated work.

This is an efficient use of resource, compound and animals, whilst integrating safety pharmacology end-points into toxicology studies.

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