

Comparison of Non-Invasive versus Invasive Telemetry

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Introduction

Historically, physiological monitoring on canine toxicity studies has been limited to recording a conventional electrocardiogram (ECG). Measurements, therefore, are restricted by practical limitations to "snap-shot" recordings (aimed at C_{max}), leaving gaps when changes in physiological parameters and any transient cardiotoxicity, particularly in the ECG parameters, would go undetected. New technological advances in non-invasive telemetry systems may allow some inclusion of quality ECG measurements for longer time periods in toxicological (or other) studies, thus reducing animal usage and compound requirements.

Study Design

Six male Alderley Park beagle dogs implanted with DSI TL11 M2 D70-PCT devices had external skin ECG electrodes placed in lead II configuration and wore jackets containing the EMKA transmitter pack. Each dog was recorded from its home pen (4.5m²) containing DSI receivers and EMKA antennae. ECGs were acquired simultaneously using both systems in freely moving animals. Increasing doses of (±) sotalol at 1-2 day intervals (4, 8, 16 mg/kg) were orally administered with control on day 1. Continuous recording on each day was 1h of baseline and 6h post-dose (sample frequency 500Hz), the same 1 min of data was reported. All data was 100% QC'd and hand-measured if appropriate.

Acceptance Criteria

Acceptance criteria for this comparison is 5% between both systems for all parameters.

Potential Differences were expected, due to:

- Slightly different lead position
- Different hardware/software
- Event marker input into each system may be 1-2 heart beats asynchronous, which may slightly affect minute averages.

Results

• Good correlation between data from EMKA and DSI systems for HR, PR, QT but not QRS

• Data for all parameters, except QRS duration, within acceptance criteria

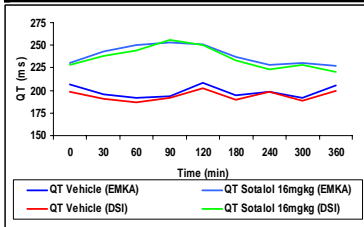
• Variation of QRS dataset on all days consistent EMKA >DSI -4ms (7-10 % approx).

• Small differences probably due to definition of QRS segment

• Peak QT_c effects (% increase of 16 mg/kg sotalol vs control)

Table 1

	EMKA	DSI
QT _{CV}	14±2	15±3
QT _{CT}	12±3	16±2



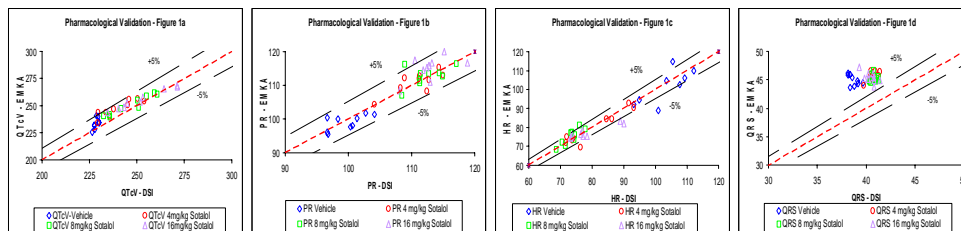
Objective

To evaluate 2 different telemetry systems; (i) invasive telemetry (DSI telemetry – acquisition and analysis Notocord HEM 3.4),

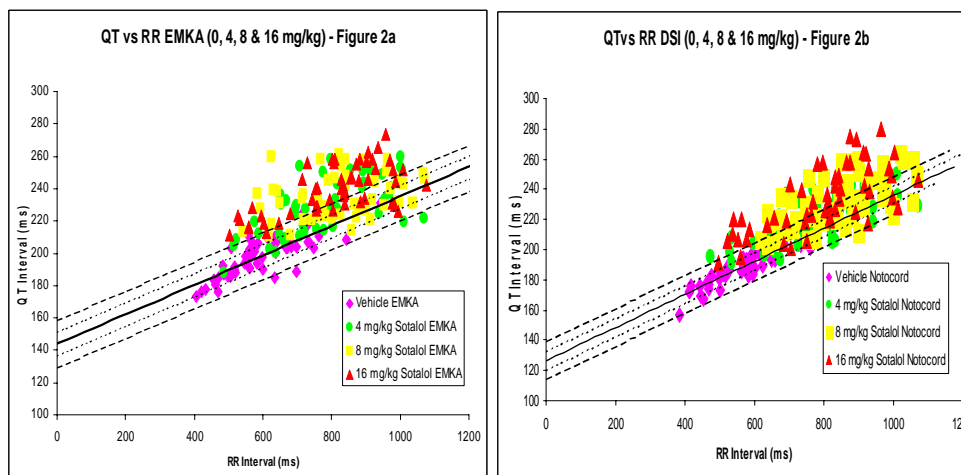
(ii) non-invasive telemetry (EMKA jacket system – acquisition and analysis IOX 1.7.0 and ECGAuto 1.5.7).

Does the EMKA system give the same results as the DSI/Notocord system with a known reference compound?

Figures 1 a-d : Correlation Plots



Figures 2 a-b : QT versus RR Plots



Conclusion

ECG data acquired by the EMKA system is complementary to DSI with the exception of QRS duration, however, the QRS differences are consistent.

The EMKA system generates high quality ECG data adding real value to toxicological and/or safety pharmacology studies.

The EMKA system will have a major impact on the 3Rs (Refinement, Reduction & Replacement).

QTcV for both systems generated a tight dose response to (±) sotalol.

However, advantages of the DSI invasive telemetry system is its combination with arterial blood pressure (and other parameters such as body temperature, left ventricular pressure/pleural pressure), permitting a complete cardiovascular core battery assessment. This allows a colony of dogs to be dedicated for Safety Pharmacology studies, with the possibility of re-use over many months.

Advantages of the EMKA non-invasive telemetry system is the lack of surgery, and thus animal welfare improvement, however, training for acceptance of jackets is required as this may induce some stress.

Additionally, for repeat-dosing Safety Pharmacology study designs (perhaps as a 'follow-up' study), a potential use would be to include these EMKA ECG measurements on specific days during an appropriate dog toxicology study (eg, 7 day repeat phase of MTD, or 28 day regulatory tox study), thus gaining a higher quality of ECG results than conventional 'snap-shot' recordings, as well as reducing the requirement for a separate telemetry study (with the animal welfare, compound requirement and resource issues associated with this).