

SENSITIVITY OF TELEMETRY TO PREDICT QT INTERVAL PROLONGATION IN DOG TOXICITY STUDIES: ASSESSMENT OF THE EFFECTS OF MOXIFLOXACIN BY INVASIVE AND NON-INVASIVE METHODS

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1 – Abstract

ECG assessment in repeat-dose toxicity studies offers important information that complements cardiovascular studies using invasive telemetry. However, the acquisition of conscious ECGs employing physical restraint may transiently alter the fundamental electrophysiology of the subject, resulting in potentially misleading results.

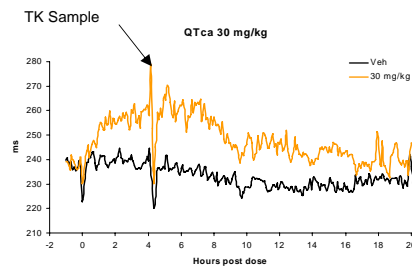
Accordingly, a variety of non-invasive jacketed telemetry systems for use in freely moving animals have been developed. The purpose of this study was to compare the sensitivity to detect moxifloxacin-mediated (MOX) QT prolongation in two groups of dogs equipped with either EMKA jacket (n=5) or ITS invasive (n=6) telemetric systems. QT was corrected for the effects of heart rate employing Van de Waters' correction (QTcV) for the EMKA system, or an individual probabilistic method³ (QTca) for ITS data. All dogs received vehicle and MOX (30 mg/kg, p.o.) and continuous L-II ECGs were obtained. To mimic the design of a toxicity study, ECGs were measured in EMKA dogs at pretest and for 6 h postdose. Dogs instrumented with ITS telemetry implants (Konigsberg) (3 male, 3 female) were dosed in a crossover design (vehicle and MOX) and ECGs were acquired for 20 h. Plasma MOX levels were measured 4 h postdose to confirm exposure and were comparable in both study groups (approx. 5.9 ± 0.6 ug/ml). MOX maximally increased QTcV by 28 ms (EMKA, threshold for significance 18 ms; $p \leq 0.05$) and QTca by 33 ms (ITS, threshold for significance 8 ms; $p \leq 0.05$). These data demonstrate that while the sensitivity to detect significant QT prolongation was slightly lower with the EMKA jacket system, both systems detected a qualitatively similar response to MOX.

Thus, the EMKA jacket system is a sensitive method to detect QT prolongation which may provide high quality ECG signals in repeat-dose toxicity studies while avoiding the confounding effects of restraint.

Moxifloxacin (MOX); synthetic fluoroquinolone antibiotic agent associated with well documented QT interval prolongation

4 – Results: Invasive Telemetry

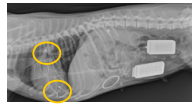
30 mg/kg: statistically significant increase of QTca from 8 ms up to 33 ms



- Individual MOX plasma levels at 4h post-dose: 6380, 6130, 5630, 5440, 4980 and 6670 ng/mL
- Mean exposure 5872 ± 633 ng/mL

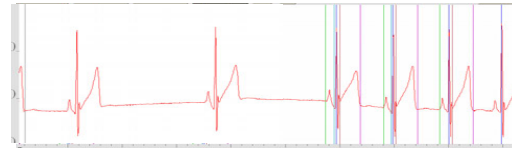
2 – Materials & Methods Invasive Telemetry (ITS)

- Three male and three female Beagle dogs (Marshall farms) received a single dose of 3, 10 and 30 mg/kg MOX in a cross-over design (including control, empty capsule); only data for the 30 mg/kg dose group are presented
- Plasma samples for TK were taken at 4h post-dose
- ITS telemetry implants (Konigsberg) in Lead II configuration



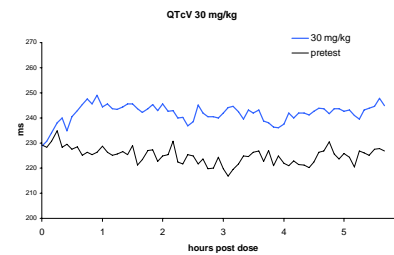
- Continuous ECG acquisition for 20h from freely moving animals
- RR, PQ, P duration, QRS, QT, and QTca (QT individually corrected) intervals and blood pressure were derived from digitized data and reported as consecutive 5 min mean values
- ECG data analyzed with CA recorder software (DISS)
- Statistics: treatment versus vehicle, ANOVA with LSD post hoc test

- Typical ITS ECG with interval markings



5 – Results Non-Invasive Telemetry (EMKA Jackets)

30 mg/kg: statistically significant increase of QTcV from 18 ms up to 28 ms



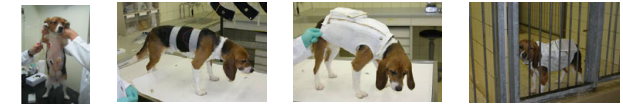
- Individual MOX plasma levels at 4h post-dose: 5890, 6600, 6050, 6570 and 4030 ng/mL
- Mean exposure 5828 ± 1053 ng/mL

Human data for comparison:

400 mg/kg MOX: QTc prolongation 5 to 10 ms (4300 ng/ml)⁴

3 – Materials & Methods Non-Invasive Telemetry (EMKA Jackets)

- Five male Beagle dogs (Marshall farms) as control (empty capsule) and five male Beagle dogs with a single dose of 30 mg/kg MOX
- Plasma TK samples at 4h post-dose
- Lead II configuration using EMKA jacket telemetry setup



- Start of continuous ECG acquisition after dosing continuing until 6h post-dose and twice pretest from freely moving animals
- RR, PQ, P duration, QRS, QT, and QTcV intervals (QT corrected by van de Water's formula) were derived from digitized waveforms and reported as consecutive 5 min mean values
- ECG data analyzed with ECG auto software (EMKA)
- Statistics: treatment versus pretest, ANOVA with LSD post hoc test

- Typical EMKA ECG trace



6 – Conclusions

- Jacket telemetry improved data quality and quantity compared to typical limb lead ECGs
- Sensitivity to detect QTc prolongation was somewhat less with the jacket system when compared to invasive telemetric ECGs, but was sufficient to accurately detect a relevant preclinical QT signal
- Jacket telemetry may be suitable for accurate QT assessment in repeat-dose studies offering a potential alternative to invasive telemetry in this setting
- Jacket telemetry fulfills the 3R criteria

References:

1. Chen X, Cass JD, Bradley JA, Dahm CM, Sun Z, Kadyszewski E, Engwall MJ, Zhou J. QT prolongation and proarrhythmia by moxifloxacin: concordance of preclinical models in relation to clinical outcome. *British Journal of Pharmacology*, 146, 792-799, 2005.
2. Van de Water A, Verheyen J, Xhonneux Reneman RS: An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *J Pharmacological Methods* 1989, 22, 207-217.
3. Holzgreffe HH, Cavero I, Gleason CR, Warner WA, Buchanan LV, Gill MW, Burkett DE, Durham SK. Novel probabilistic method for precisely correcting the QT interval for heart rate in telemetered dogs and cynomolgus monkeys. *J Pharmacol Toxicol Methods*. 2007;55:159-175.
4. Balfour JA and Wiseman LR: Moxifloxacin. *Drugs*, 57, 363-373 (discussion 374).