

Comparisons of EMKA Jacket System and DSI Implant in Conscious Dogs with Moxifloxacin



Hai Ming Tang, Alvie Bello, Chris Lawson, Bluegrass Biggs, Vicki Garcia, Sushmita Chanda, Kyle Kolaja, Stefan Platz, Christina Riordan, and Dinah Misner

Department of Non-Clinical Safety, Roche Palo Alto

Abstract

Introduction: We compared the EMKA jacket system and DSI implant in same animals to determine sensitivity to detect QTc prolongation using moxifloxacin as a positive agent. **Methods:** Four beagle dogs (2M/2F) were surgically instrumented with DSI telemetry implants, and limb lead II ECG and blood pressure monitored. Animals were jacketed after they were shaved and seven lead surface ECG configurations (limb I, II, III, aVR, aVL, aVF, V) and activity were continuously recorded with the jacket system. Following 1 hr of baseline recording, moxifloxacin (30 mg/kg) or placebo was administered orally. Cardiovascular parameters were continuously recorded for 6 hr post dose. **Results:** Moxifloxacin significantly increased QTc interval compared to placebo group with maximum QTc prolongations of 48 and 39 ms for the jacket system and the implant, respectively. No effects on PR, QRS and BP were observed following moxifloxacin. In addition, different ECG waveform morphology (e.g. positive vs negative T-wave) were noted between jacket and telemetry implant. **Discussion:** ECG signal quality from the EMKA jacket system was equal or even superior to that of the DSI implant. The jacket system was also slightly more sensitive than implant in detecting QTc prolongation. These differences between the 2 systems may result from the combination of higher signal quality with the jacket system and sub-optimal placement of subcutaneous ECG leads with the DSI implant. In summary, the EMKA jacket system is robust and sensitive in detecting QTc prolongation and provides high quality ECG signals.

Introduction

Telemetry implants have been widely utilized in assessing safety liabilities of new chemical entities (NCEs), especially on ECG abnormality (e.g. QT prolongation). While being the gold standard in safety pharmacology, such approaches are not perfect. Limitations include potential animal well-being concerns (e.g. infections), invasive surgeries, limited ECG lead configuration, telemetry device failure, limited battery life, etc. More recently, non-invasive, telemetry jacket systems have become available and provided an alternative method in monitoring ECG parameters in conscious animals. The goal of this study was to compare the EMKA jacket system and DSI implant in same animals to determine each system's sensitivity in detecting QTc prolongation using moxifloxacin as a positive agent.

Methods

Animal Preparations

Four beagle dogs (2M/2F, weight range 9 - 11 kg) were used in this study. All procedures related to the use of animals in these studies were reviewed and approved by the institutional animal care and use committee (IACUC) at Roche Palo Alto. The animals were surgically instrumented with DSI telemetry implants (TL11M3-D70-PCTP). The animals were fasted overnight prior to each experiment. On each experimental day, animals were shaved and surface ECG electrodes (4 limb and 1 chest leads) attached. Animals were then to wear specially-designed jackets to protect ECG electrodes and lead wires and returned to their cages. Vital signs of each animal (e.g. blood pressure, heart rate, QTc, body temperature) were monitored and recorded every 50-70 minutes throughout the experiment. At the end of each experiment, the surface ECG electrode patches and jackets were removed and animals returned to their home cages.

Study Design

Four beagle dogs (2M/2F) were randomly assigned to receive either a single dose placebo or moxifloxacin (30 mg/kg, p.o.) during Week 1 and Week 2. Each animal received both treatments (placebo and moxifloxacin) with a 6-day washout period between treatments. Moxifloxacin was administered orally via capsule at 30 mg/kg. Placebo-treated animals received an empty capsule.

After ECG signals were stabilized, baseline cardiovascular parameters (BP, HR, ECG) were recorded for 60 minutes prior to dosing and continuously recorded for another 6 hours post dose.

Methods (Continued)

Drugs and Formulations

Moxifloxacin was purchased from Sequoia Research Products (Berkshire, UK) and weighted into capsule on each experimental day.

Data Collection and Analysis

Jacket System: 7 lead ECG (Limb I, II, III, aVR, aVL, aVF, V) and activity were recorded via IOX data acquisition software (EMKA Technologies, Falls Church, VA). **Implant System:** Limb lead II ECG and blood pressure were recorded via Ponemah data acquisition software (DSI, Valley View, OH). ECG-AUTO (EMKA Technologies, Falls Church, VA) software was used for ECG analysis in both systems. Van de Water formula $QT_{c} = QT_{ms} - 87 \times (RRs - 1)$ was used to correct the QT interval for the variation of the RR interval.

Plasma Drug Concentration

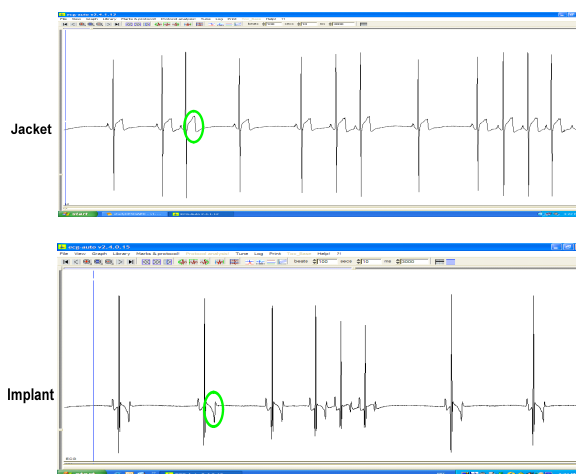
For the determination of the plasma concentration of moxifloxacin, 1 ml venous blood samples were taken at pre-dose and 6 hours post dose. The blood samples were centrifuged at 3,500 rpm for 7 min at 4°C. The plasma was stored at -20°C until the drug concentration was analyzed by the Department of Drug Metabolism and Pharmacokinetics of Roche Palo Alto.

Statistical Analysis

At each time point, the moxifloxacin-treated group was compared to the respective placebo group using two-way repeated-measures analysis of variance (ANOVA) model including terms of dose and animal. A value of $p < 0.05$ was considered statistically significant.

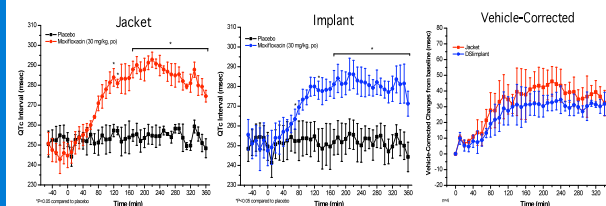
Results

Figure 1. Comparison of ECG (Lead II) Morphology in Jacket vs Implant (Dog A)



Results (Continued)

Figure 2. Moxifloxacin (30 mg/kg, p.o.) Prolonged QTc Interval



Summary

- Excellent ECG quality from the jacket system
- ECG parameters in placebo group stable during the 6-hr period
- Absolute baseline QTc values identical between jacket and implant
- Moxifloxacin significantly increased QTc interval compared to placebo group (ΔQT_{cmax} of 48 and 39 ms for jacket and implant, respectively)
- QTc effect well sustained during the 6-hr period
- Jacket system is slightly more sensitive than implant in detecting QTc prolongation
- No effects on PR, QRS and BP were observed following moxifloxacin (data not shown)
- Different ECG waveform morphology between jacket and implant (i.e. positive T-

Discussion

ECG signal quality from the EMKA jacket system was equal or even superior to that of the DSI implant. This finding could be explained by higher signal quality from the jacket system and sub-optimal placement of ECG lead (especially with subcutaneous leads placement) with the implant. The differences in signal quality contributed to the higher sensitivity in QTc signal detection from the jacket system than implant.

The mean moxifloxacin plasma concentration of 6000 ng/ml at 6-hr post dose is consistent with the literature ($C_{6hr} \sim 6500$ ng/ml following 30 mg/kg p.o.)^{1,2}. The onset of QTc prolongation in the study (~ 2 hr) is also consistent with the T_{max} of 2.5 - 3 hr for moxifloxacin in dogs^{1,2}.

In conclusion, the EMKA jacket system is robust and sensitive in detecting QTc prolongation in conscious dogs.

References

1. Chen X., et al. QT prolongation and proarrhythmia by moxifloxacin: concordance of preclinical models in relation to clinical outcome. Br J Pharmacol 2005 146, 792-799.
2. Chaves A.A., et al. A highly sensitive canine telemetry model for detection of QT interval prolongation: studies with moxifloxacin, haloperidol and MK-499. J Pharmacol Toxicol Meth 2007 56, 103-114.