Development of A Large Animal Model for Combined Seizure and Cardiovascular Liability Assessment

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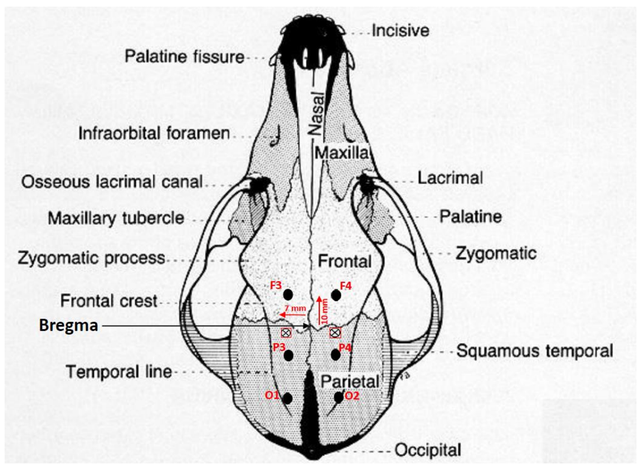
1 INTRODUCTION

Evaluation of central nervous system (CNS) liabilities is traditionally limited to behavioral assessments. However, due to the growth in compounds targeting CNS indications and novel approaches for delivering drugs to the CNS, the need for more sensitive CNS assessments has arisen in recent years. Regulatory agencies are now routinely requesting electroencephalography (EEG) studies be conducted especially with continuous monitoring. These assessments have predominantly been conducted using analogue telemetry, which are limited to 2 EEG leads. However, advances in digital technology can now improve sensitivity and expand assessments that can be conducted within a single model. The objective of this study was to examine the feasibility of a dog model implanted with telemetry implants for concurrent assessment of EEG, ECG and blood pressure (BP).

2 METHODS

Six Beagle dogs were implanted with digital telemetry system consisting of the EMKA easyTEL+ L_EEEETA (3-lead EEG) and easyTEL+L_EPTA (ECG and BP) probes.



Lead placement:
EEG: 3 leads (frontal, parietal and occipital), and electromyography (EMG) lead on neck (*Schematic diagram adapted from Evans and Christensen, 1979)*

ECG: Lead 2 configuration, with one lead fixed on the apex of the heart and the other attached to the right atrium. the blood pressure catheter was inserted in the left femoral artery.

Seizure liability assessments (EEG):

- Each dog received an intravenous infusion of pentylenetetrazol (PTZ) at a rate of 1.5 mg/kg/min (0.03 mL/kg/min), to induce a rapid onset of seizure activity.
- Intravenous injections of Diazepam at 1 mg/kg were immediately administered to terminate the convulsions.
- Video-EEG data were collected throughout the monitoring period.
- EEG data were visualized directly using emka TECHNOLOGIES post-processing software ecgAUTO-EEG+.

Cardiovascular liability assessments (ECG, BP):

- Each dog received a single oral dose of Moxifloxacin at either 30 or 90 mg/kg (n=3/group), to induce a prolongation in QT.
- Heart rate, arterial blood pressure (systolic, diastolic, and mean pressures), ECG parameters (PR, QRS, RR, QT and heart rate-corrected QT interval), and body temperature were monitored.
- QT was corrected using the Van de Water equation (QTcv = QT-87(60/HR-1))
- ECG data were analyzed using emka TECHNOLOGIES post-processing software ecg AUTO.

For each assessment, data were collected continuously for at least 24 hours prior to dosing (baseline; intended for signal quality verification and to assess each animal's normal EEG/EEG). On the day of dosing, collections were started prior to dosing, and continued during the dosing procedure through at least 24 hours postdose.

3 RESULTS

Seizure liability assessments

Administration of PTZ at 1.5 mg/kg/min produced seizures and prodromal EEG abnormalities confirming the appropriateness and sensitivity of the model for use in seizure liability studies. Stereotypy (e.g. licking, chewing), tremors, tonic contractions, mild myoclonus, agitation and salivation were noted on video during periods with prodromal EEG abnormalities.

Animal No.	Start of prodromal EEG (min postdose)	Start of seizure (min postdose)
1101*	20	26
1102	6	23
1103	10	35
1104	8	10
1105	20	27
1106	10	26

*PTZ infusion rate was first administered at 0.025 mg/kg/min for ~55 min, with only minimal effects. Infusion rate of 1.5 mg/kg/min was restarted and effects are indicated in the table.

Table 1: Onset of Seizures and Prodromal EEG Abnormalities. Administration of PTZ at 1.5 mg/kg /min produced seizures starting between 10 and 35 minutes postdose. Prodromal EEG abnormalities indicative of increased risk of seizure were noted starting 6 to 20 minutes postdose.

3 RESULTS (Cont'd)

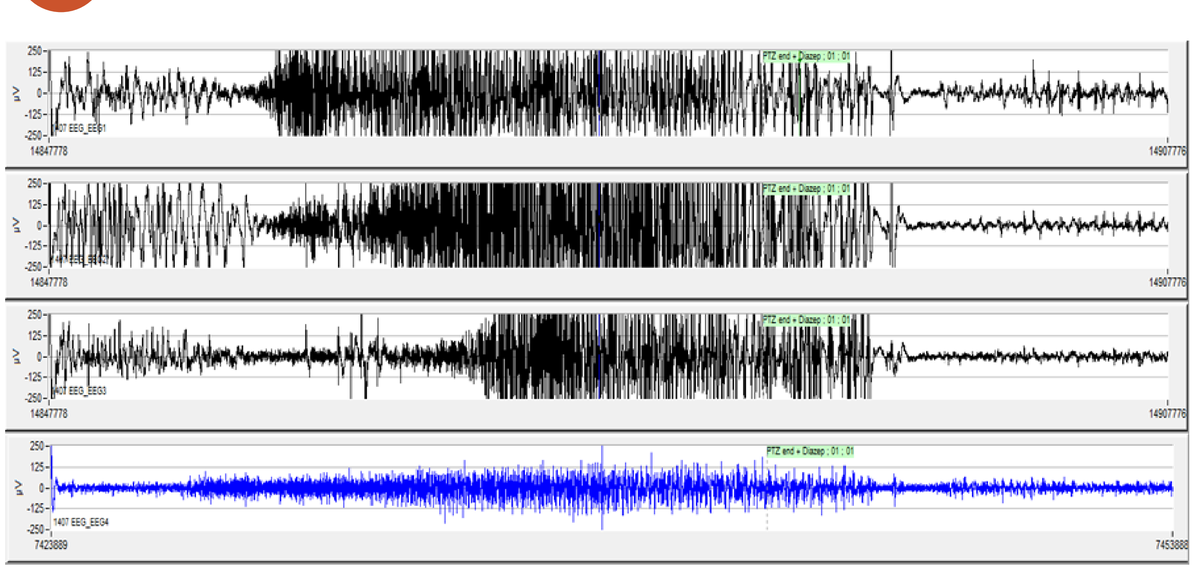


Figure 1: Example of PTZ-induced seizure with tonic-clonic correlates (Animal 1104). Frontal onset (EEG1) of paroxysmal activity is captured in succession by EEG2 and EEG3. Brief postictal attenuation. (from top to bottom: EEG1, EEG2, EEG3, EMG; 60 sec).

Cardiovascular liability assessments

Administration of Moxifloxacin at 30 and 90 mg/kg induced a QT interval prolongation, confirming the appropriateness and sensitivity of the model for use in cardiovascular liability studies.

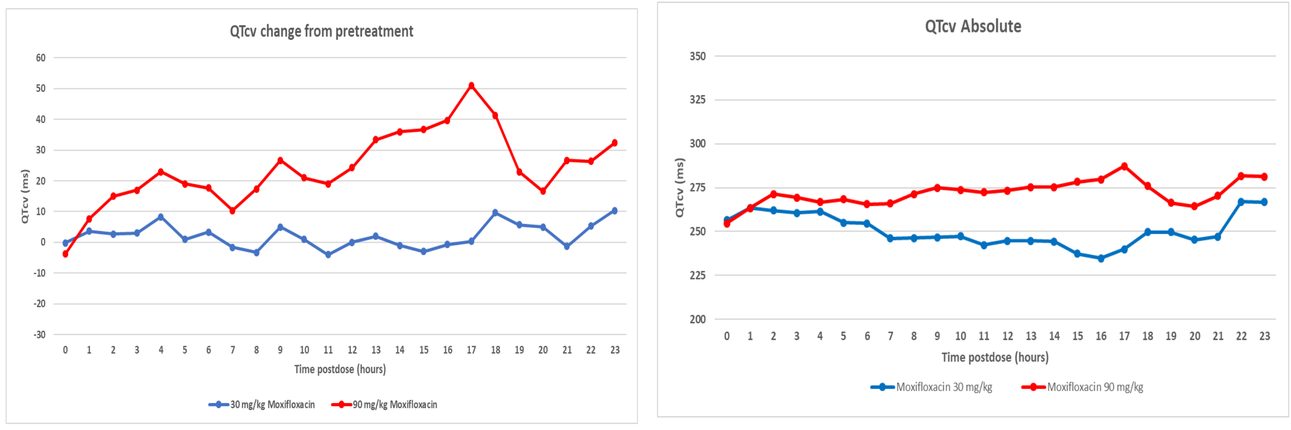


Figure 2: Treatment with Moxifloxacin at 30 and 90 mg/kg induced QT interval prolongation (left; change from pretreatment, right; absolute).

Combined assessments

With the use of two telemetry implants, cardiovascular and neurological signals can be synchronized and visualized post collection. The synchronization and quality of all signals were confirmed for all collections.

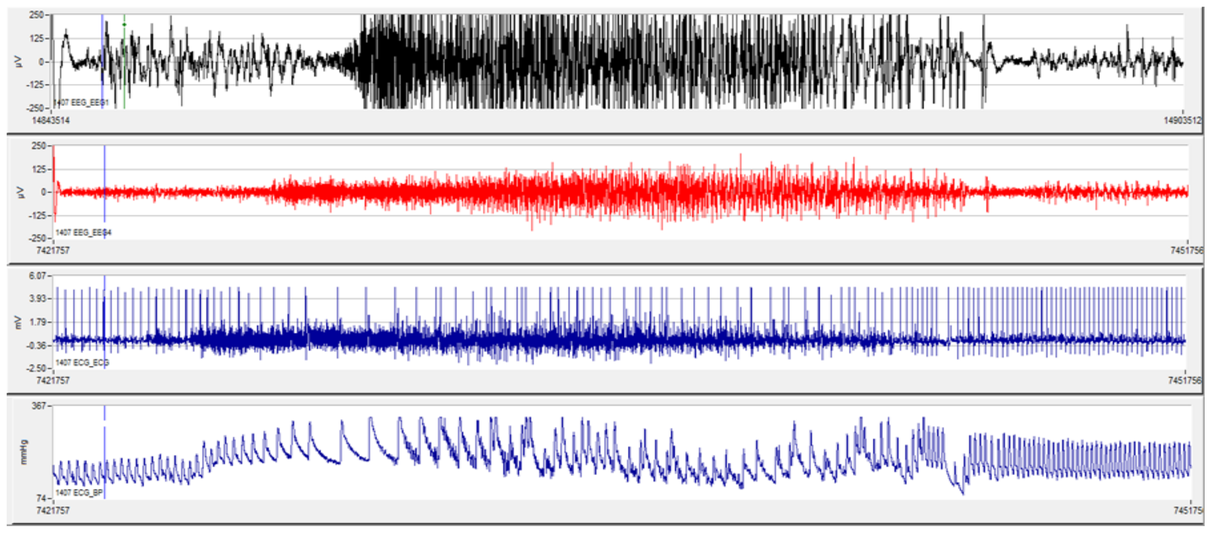


Figure 3: EEG/ECG signal synchronization. Increased BP and ECG/QRS abnormalities correlated with a seizure (animal 1104, from top to bottom: EEG1, EMG, ECG, BP; 60 sec).

4 CONCLUSION

Administration of PTZ and Moxifloxacin induced the expected physiological changes with induced location-specific prodromal EEG and frank seizures and QTc prolongation supporting the sensitivity of the model.

Through the application of two telemetry devices simultaneous EEG and cardiovascular assessments can be conducted in parallel in a single model reducing animal numbers and improving model sensitivity to detect potential drug related cardiovascular and CNS effects.