Surface Lead EEGs: Will It Stick?

Ken Kearney[1]; Courtney Jenkins[1]; Nick Adkins[1]; Cory Appleby[1]; Monica Metea[2]; Chelsea Richardson[3]; Brian Roche[1]

1 Charles River Laboratories
2 Preclinical Electrophysiology Consulting
3 EMKA Technologies

1 ABSTRACT

Clinical CNS findings continue to be a leading cause of late stage drug attrition. While increased focus has driven earlier characterization for CNS risk, often potential for CNS adversity continues to be characterized later in the IND enabling studies. One factor driving this trend is the cost and timing associated with evaluation of implanted telemetry.

The current study investigated the feasibility to evaluate potential CNS risk (lowered seizure threshold) using an external telemetry system employing subdermal needle electrodes and pediatric adhesive button electrodes (EMKA rodentPACK [eegPACK]) in two bipolar recording configurations that sampled the frontal and temporal regions. The sensitivity of the EMKA eegPACK was compared to a validated implanted DSI telemetry device sampling the frontal and temporal regions with biopotentials placed on the dura. Pentylenetetrazol (PTZ) was administered intravenously at a rate of 1.5 mg/kg/min in two male beagle dogs until emergence of premonitory biomarkers of reduced seizure threshold (isolated and/or organized sharp waves, increased synchrony, myoclonic discharges, etc.) and subsequent electrographic seizure.

The EMKA eegPACK demonstrated comparable sensitivity between the needle and pediatric button electrodes. While the system presented an expected dampened amplitude compared to the implanted telemetry, the EMKA eegPACK presented adequate sensitivity to detect altered EEG (synchrony, sharply contoured waves, and organized sharp waves) and frank seizurogenic episodes using button electrodes. Although it is not anticipated to fully replace implanted dural telemetry (provided identified issues can be adequately addressed), the system sensitivity (as well as flexibility to allow for use in restrained or ambulatory environments) has warranted its potential for screening applications in the CNS arena.

2 INTRODUCTION

Currently, the evaluation of EEG may be assessed through the use of 2 primary platforms: restrained subdermal model or surgically implanted telemetry. Restrained subdermal evaluations are most beneficial for prescreening applications (to eliminate animals with underlying predispositions to lowered seizure threshold) or for investigation of compounds with a known window of convulsive risk. Surgical implants offer continuous assessment of EEG with greater signal reliability for chronic evaluations when the potential period of risk is unknown or not repeatable among all subjects.

The intent of this study was to evaluate a new device to bridge the gap between acute and chronic assessments to evaluate seizure potential when the time of insult is unknown. The EMKA eegPACK was evaluated for potential use in acute assessments or for moderate durations of ambulatory evaluation, without the need for surgical implantation. In the restrained state, the animals are susceptible to noise in the EEG waveform from excessive struggling due to agitation from restraint. In the ambulatory state, the animals are able to freely move about their home cages without the additional stresses associated with the restraint system.

In a prior internal investigative study, the use of needle electrodes vs. pediatric, adhesive surface electrodes were evaluated. Both electrodes provided equivalent signal quality. As the pediatric button electrodes allowed for potential use in an ambulatory environment, this electrode was utilized in this study.

3 MATERIALS AND METHODS

- 2 male Beagle dogs approximately 10 months old and weighing approximately 9.2 kg were used as the test subjects.
- Animals were previously implanted with DSI D70-EEE transmitters
  - 2 bipolar EEG leads were placed equidistant to bregma; 1 lead was placed in the neck muscle for evaluation of EMG
- Animals were sufficiently acclimated to sling restraint
- Baseline data were collected for approximately 10 minutes prior to dosing.
- Pentylenetetrazol (PTZ) was infused at 1.5 mg/kg/min using calibrated infusion pumps.
- The animals were monitored continuously during the infusion. At the sign of first sign of clear paroxysmal activity or convulsive phenomena were observed, PTZ infusion was stopped and Diazepam (1 mg/kg) was injected and administered to effect by a staff veterinarian.

Implanted Telemetry System:

- Telemetry data were relayed from the EEG device using a single RMC-1 receiver connected to a data exchange matrix using the DSI Ponemah Physiology Platform (P3) data acquisition software (V5.2) .
- All EEG and EMG signals were collected at 500 Hz.
- Time matched video data were acquired using Axis 221 network cameras (resolution setting of 480x360 at 30 frames per second); interfaced with the video module within P3.

External Telemetry System:

- Telemetry data were transmitted via Bluetooth using the EMKA eegPACK v3 transmitter encased in a fitted ambulatory cap atop the subjects head (Schematic 1).
- Signals were collected using disposable pediatric adhesive electrodes with 2 lead set-ups (placement mimicked the implanted EEG configuration)
- Data were collected using IOX2 (v. 2.10.4.8) sampled at 1000Hz
- Video data were acquired using 1 FOSCAM camera and an EDS14 NAS (for video storage and synchronization).

4 RESULTS AND DISCUSSION

PTZ effects were initially investigated in detail using implanted telemetry and NeuroScore (DSI). Administration of PTZ produced seizures in two animals at 19 and 21 minutes postdose, respectively. Prodromal behavioral observations correlated with EEG abnormalities indicative of increased risk of seizure were noted and included salivation, increased swallowing, agitation, tremors, tonic contractions and stereotypy (chewing). Prodromal EEG abnormalities indicative of increased risk of seizure consisted of isolated sharp waves (ISW) or organized sharp waves (OSW) and repetitive bursts of high frequency EEG (low gamma). Stereotypy and tonic contractions were noted mostly during high frequency discharges, while OSWs and ISWs were generally associated with mild myoclonus. Diazepam was administered shortly after the onset of each convulsion, effectively interrupting the tonic-clonic events. Postictal attenuation with residual epileptiform activity was noted for ~30 sec after the end of each frank seizure, followed by EEG slowing.

The EEG channel 1 of the EMKA eegPACK external system retained sufficient EEG for analyses of frank seizures, however, low amplitude noise contamination confounded the detection of prodromal EEG such as sharp waves and/or slowing during periods of excessive excitation/movement (Figure 1). EMKA eegPACK data were sampled at 1000 hz (in opposition to DSI data sampled at 500 hz) in an effort to minimize potential of missing a ISW due to sample rate limitations. The difference in sampling rate may however have introduced greater high frequency noise, thus impeding detection of these biomarkers. In absence of significant motion artifact, the system demonstrated sensitivity to capture biomarkers of lowered seizure threshold (ISW/OSW) (Figure 2).

Synchronization of video with RAW data traces and display issues were identified with the EMKA eegPACK external system and were communicated to the vendor, for suggestions of future improvements.

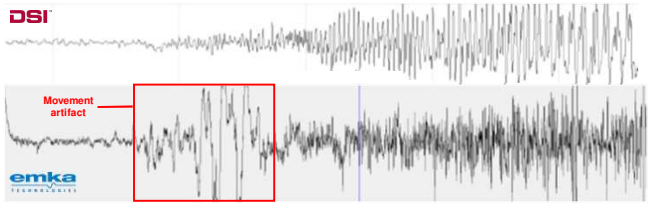


Figure 1. Onset of seizure with implanted collections (DSI, upper figure showing Channel 1EEG) and EMKA eegPACK collections (EMKA, lower figure showing channel 1 EEG) (10 sec; ±100 µV). Movement artifact confounded detection of prodromal biomarkers preceding the seizurogenic episode.

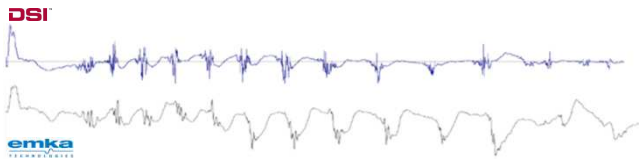
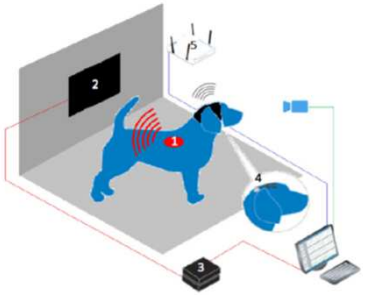


Figure 2. Immediately following second dose of diazepam and termination of seizure. Post ictal period compared directly between the two collection systems (upper trace represents DSI channel 1 EEG; lower trace represents EMKA channel 1 EEG) (5 seconds; ±200 µV). In absence of excessive movement and agitation, the EMKA eegPACK demonstrated adequate sensitivity to capture biomarkers of altered EEG (OSW).

In conclusion, based on reviewing portions of EMKA artifact-free data, it was concluded that the external collection system is adequate for the intended scope, provided issues identified are addressed. Recommendations were made for optimization of lead placement, securing on the skull, reducing susceptibility to noise and improvement of the analysis tools. Optimization of setup and analysis tools will increase the sensitivity of the system and render it adequate for screening purposes. The current beta version is adequate for identifying seizures (Figure 1) with future potential for prodromal screening (Figure 2).



Schematic 1. Schematic represents collection hardware for each system. (DSI Hardware: **1**. D70-EEE implant **2**. RMC-1 receiver **3**. Data Exchange Matrix.) (EMKA Hardware: **4**. EMKA eegPACK **5**. Digital Receiver)