

Introduction

Electroencephalography (EEG) studies are periodically required as follow-on studies to safety pharmacology core battery (S7A requirements). It is critical to differentiate CNS adverse effects from peripheral toxicity. Proconvulsant risk evaluations are routinely conducted in rodents and the results often necessitate further development in non-human primate models. In this study, video-EEG monitoring proved to be useful in characterizing neurological adverse effects with unpredictable onset, and computerized video-EEG analysis was used for proconvulsant risk assessment, spectral analysis of frequency bands, and sleep stage determination (Authier, 2009).

The Challenge

If a new drug candidate induces life-threatening adverse effects such as generalized seizures, it is crucial that the underlying mechanisms be well understood and characterized, or drug development could be halted. Classification of adverse events can be complex and challenging due to the difficulties in determining whether drug-induced muscular contractions are from centrally or peripherally neurological alterations (Lahunta, 2006). Adverse event onset can be unpredictable, making monitoring and detection vital, whether the involuntary skeletal muscle contractions are resulting from centrally mediated toxicity, or a neuromuscular transmitter disorder. While video-EEG monitoring has been a standard diagnostic tool for humans (Asano, 2005), this study investigates a novel application of continuous video-EEG monitoring and computer EEG analysis to qualify seizure detection in a non-human primate model.

The Solution

The researchers deployed the use of wireless telemetry implants and EEG-video monitoring to obtain 24 hours of continuous baseline data.

The Study

Three cynomolgus monkeys were prepared with telemetry transmitters (TL11M2-D70-EEETM, Data Sciences International, Saint Paul, MN USA) and EEG electrodes placed, based on the 10-20 system (C3-O1, Cz-Oz, and C4-O2), all in accordance with the guidelines and principles outlined in the current *Guide to the Care and Use of Experimental Animals*. EEG-video monitoring included a digital color camera equipped with daylight and infrared night vision connected to a computer housing the analysis software. 24 hours of continuous baseline data confirmed that synchronous video and EEG were being collected prior to treatment. Treatment of subcutaneous pentylene-tetrazole (PTZ 10 mg/kg, 0.1 mL/kg) continued about every 15 minutes until seizures were noted. When clonic convulsions were observed on video, a single diazepam injection, administered IV (1.0 mg/kg) was sufficient to terminate seizure and paroxysmal EEG activity in all animals. Video and EEG were continuously recorded for 20 hours after diazepam administration.

Results and Successes

PTZ administered at 15-minute intervals until clonic convulsions were noted confirmed the method of computerized seizure detection. Paroxysmal activity was detected at least 4 minutes before general seizure in all animals. The NeuroScore (Data Sciences International, Saint Paul, MN USA) seizure detection module identified spike trains during seizure in all animals (Fig. 1). Synchronized video was used to differentiate jerky movements and clonic convulsion from artifacts such as EMG.

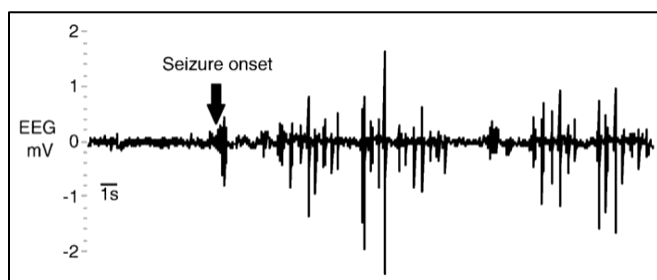


Figure 1: A spike train detected using NeuroScore seizure detection software from a freely moving, telemetry

The software accurately identified the spike train events in all animals from 44 hours of EEG tracings, which facilitated data processing. Software sensitivity to detect spike trains was high (EEG review confirmed that all spike trains had been identified) while specificity was low (a large number of EEG segments identified as spike trains by software were excluded following video and EEG review). Computer analysis significantly reduced the amount of EEG traces to review for spike trains to less than 5 min per 24-hour period.

It remains that correlation of spike trains with behavioral activity recorded on video by a trained reviewer was required for interpretation of EEG traces.

Some drugs have a relatively slow absorption rate and several hours may elapse between administration and onset of adverse events. It is not always possible or ethical to restrain animals until an adverse event occurs. Continuous EEG monitoring can generate a large volume of raw data that may render manually reviewed EEG impractical. In these cases, synchronized video and EEG combined with computerized EEG analysis may be used to help:

- characterize neurological clinical signs with unpredictable onset
- determine underlying mechanisms of adverse events so that drug development may proceed
- reduce and optimize data processing
- facilitate evaluation

While most studies use rats and mice, pharmacological and pharmacokinetic considerations may support using non-human primates in some cases and this pilot study establishes standards of video-EEG with computerized analysis in cynomolgus monkeys.

Data Sciences International

Data Sciences International (DSI) has been committed to life science research for over 30 years and is the proven leader in preclinical physiological monitoring. DSI offers complete systems that sense, transmit, acquire and report physiological data. Each system is engineered with quality and performance you can trust. The DSI team ensures that researchers are equipped and prepared from the first minute of their study to the last; because your research is everything.

References:

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