Safety Pharmacology Society Webinar
Seizure Liability Testing in Nonclinical Studies: Management and Regulatory Considerations

Pre-study EEG evaluations - the importance of selecting “normal” animals and of ruling out increased seizure liability

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Increased interest in pre-clinical EEG as a tool to identify the effects of experimental compounds on seizures

Not all seizures result in convulsions and not all convulsions are due to seizure

Seizure risk may be underestimated due to their time of occurrence (e.g., night time), brief duration (e.g., 20 seconds) or type (e.g., partial seizure or absence seizure)
Increasingly, pre-clinical EEG has been used to rule out seizure in the face of suggestive behaviors (i.e., repetitive tremors)
The focus of this presentation is to outline the value and feasibility of pre-study screening of subjects for abnormal EEG patterns

- Altered seizure threshold
- Japanese cartoon
- Stress, imbalance, fatigue, sleep, foods, etc.
- Change in brain chemistry or in the balance between excitation and inhibition - interacts with real life
- Dogs have a high incidence of seizures
Clinical EEG – 100 year history
Identification of “spikes” or sharp waves – key to identification of increased seizure risk

Fig. 1. The first seizure of a 4-year-old boy, occurred during sleep and was marked by tonic deviation of the head and eyes to the left side, followed by generalized tonic-clonic convulsion and vomiting, lasting about 10 min. The EEG shows focal spikes in the right occipital area with less involvement of the right parieto-temporal area.
Pre-study Assessment of EEG

- Non-invasive – subcutaneous electrodes
- No surgery – relatively little expense
- Sampling of EEG from multiple sites and at multiple time points
- “Abnormal” EEG patterns can occur in the absence of behaviors
Normal pattern of EEG (monkey) – three channels (frontal, temporal/parietal and occipital) – rich mixture of frequencies and amplitudes
isolated sharp waves

multiple sharp waves
Paired sharp waves

Repetitive organized sharp waves
Repeating pattern of sharp waves (abnormal circuit)
Complex pattern of sharp waves

asymmetric facial grimace
Increased synchrony in the absence of sharp waves

Graph showing wave patterns over time with labels Fz-Cz, Cz-T2, and 0-22 in uVolts.
Pre-study evaluation of EEG

- Unexpected seizure in low-dose dog
- Spontaneous seizure rate in dogs related to breed – approximately 4%
Baseline assessment – subject was removed from study prior to dosing
Sharp waves
Example of pre-study EEG screening with no “positive findings” – two separate baseline assessments

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<th>Increased Sharp Waves</th>
<th>Repetitive Bursts of Sharp Waves</th>
<th>Partial Seizure</th>
<th>Generalized Seizure</th>
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Conclusions:

- There is clear value in identifying “abnormal” EEG patterns prior to dose administration.
- Pre-study EEG evaluations are feasible in mice, rats, dogs and monkeys.
- Studies in dogs are especially important as select breeds have a relatively high spontaneous seizure rate (approximately 4% in beagles).
- Pre-study EEG evaluations can be done using non-invasive techniques and at a relatively low cost.