
Video-EEG for seizure liability evaluations and establishing safety margins

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Seizure Liability: A Broad Perspective

“All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison.” Paracelsus
Seizure Liability: A common concern

List of products associated seizure:
- Water intoxication
- Tea (i.e. theophylline)
- Stimulants (e.g. dexedrine)
- Antihistamines (e.g. diphenhydramine)
- Cyclic antidepressants
- Bupropion (smoking cessation treatment)
- Isoniazid (treatment for tuberculosis)
- Analgesics (e.g. tramadol)
Why use Video-EEG Monitored by Telemetry…

- Onset of abnormal EEG or seizure is unpredictable
- Video-EEG is the **gold standard** for clinical trials
- Significantly reduces EMG artifacts
- Video → **Behavioral** signs are paramount to seizure liability interpretations
Seizure Liability... Careful Planning

- If associated with clinical hold, **submit** your seizure liability design to **regulators** for review

- **Plasma** drug concentrations are critical
  - Consider remote blood collections to avoid EEG artifacts

- **Avoid** **Beagle dogs** when possible
  - Regulators will typically accept a change in species for follow-up

- Sequence of **premonitory signs** in animals is valuable ... but it may not match humans
Seizure Liability… Careful Planning

● What is the **ideal** administration **route**?
  - **IV** formulations → CNS assessments with progressive exposure
  - **PO** dosing: Unknown plasma level, single dose level per occasion

● Are drug induced seizures **self-limiting**?
  - Average seizure duration <1 min

● Are **emergency** anti-convulsive **treatments** successful?
  - Valuable for clinicians for human trials (diazepam, propofol, phenytoin)
Seizure Liability… Careful Planning

- What is the typical group size?
  - Rodents: 5 to 10 animals per group
  - Non-rodents: 4 to 8 animals per group

- What is the typical design scheme?
  - IV dosing: Staff ratio sufficient to intervene (1 staff for 1 animal)
  - PO dosing: Include continuous and remote monitoring around Tmax
Seizure Liability… Careful Planning

● What is the typical design scheme?
  - Dose escalation preferred with vehicle/control given first
    ● Avoid kindling: recurrence is more likely once seizure occurred
  - Highest dose may or may not induce seizure: Safety margins
  - Repeat dose/exposure can be required
    ● Based on previous seizure events with test article
  - Wash-out similar to other SP studies (calculated using half-life)
Which Data to Capture?

- **Science driven choices…**
  - EEG: multiple derivations (10-20 system)
    - Cz-Oz
    - F3-C3
    - C3-O1
    - C4-O2
  - EMG: Sleep scoring and artifacts
  - ECG: Help characterize the AE (e.g. syncope or seizure?)
  - EOG: Sleep scoring
  - Video = A critical component
Should we include Positive Control(s)?

- Not required systematically…
  - If the model is well qualified
  - Comparison with vehicle/control treatment

- Sometime useful to:
  - Demonstrate validity of the model to regulators
  - Confirm sensitivity for seizure and precursor signs

- When re-using animals (i.e. large animals) include positive control as last treatment
  - Avoid kindling
Positive Control: Seizure Detection Studies

EEG in a Cynomolgus monkey receiving PTZ (Cz-Oz)

Seizure onset

Average PTZ convulsive dose: 48.3 mg/kg
Positive Control: Seizure Detection Studies

EEG in a Beagle dog receiving PTZ (Cz-Oz)

Average PTZ convulsive dose: 31.2 mg/kg
Positive Control: PTZ Rat Model

- **1st Myoclonus**
- **1st Clonic convolution**
- **1st Tonic convolution**

**PTZ dose (mg/kg)**

- **Saline**
- **Yohimbine 18 mg/kg**

* p < 0.05
EEG Analysis Strategy

- Computerized analysis
  - Automated seizure detection module
    - Rapid **screening** of the entire dataset
    - High **throughput** but very low specificity
  - Spectral analysis: Sedation or stimulation
- Include expert review of EEG data
  - Based on **pharmacokinetics**
  - At time of selected clinical signs (tremors, ataxia, etc.)
Relative pre-ictal changes in power bands in telemetered cynomolgus monkeys

- Delta (0.5-4 Hz)
- Theta (4-8 Hz)
- Alpha (8-12 Hz)
- Sigma (12-16 Hz)
- Beta (16-24 Hz)
Polysomnography

- Drug Induced Sleep Disturbances
  - Aging increases stage 1 sleep and decreases Stage 3
    - Increased susceptibility in populations receiving polypharmacy
  - Sleep apnea = greater risk of all-cause mortalities
  - Prescription drugs can alter sleep in several ways:
    - Change to sleep architecture
    - Nightmares & insomnia (CV drugs)
    - Nocturnal asthma
REM in Cynomolgus Monkeys (n=5)

- Water/Control
- Caffeine 0.3 mg/mL
- Caffeine 1 mg/mL
- Caffeine 3 mg/mL
NREM Stage 3 in Cynomolgus Monkeys (n=5)

- Water/control
- Caffeine 0.3 mg/mL
- Caffeine 1 mg/mL
- Caffeine 3 mg/mL

Duration (min) vs. Zeitgeber time (h)
Spectral Analysis: Diazepam (PO, 2 mg/kg) Cynomolgus Monkeys (n=5)
Conclusions

- Video-EEG using telemetry capture high quality EEG tracings with concurrent video for behavioral interpretations.

- Positive controls are not essential in follow-up studies but can be useful.

- EEG combination studies can be considered:
  - Polysomnography, sedation/stimulation and seizure.
Questions

Join us in Washington for the Annual SPS meeting!