Characterization of EEG Morphologies During Drug-Induced Seizures and Peri-Ictal Changes in Non-Clinical Species

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INTRODUCTION

Regulatory agencies require that the most sensitive species be used for seizure liability assessment during drug development. A broad range of automated and manual methodologies are available to detect or identify ictal and inter-ictal events in non-clinical EEG obtained by telemetry. The strategy to detect seizure events is often based on EEG morphology and defining those events is essential to ensure appropriate algorithm selection. The current study aimed to analyze EEG morphologies observed during drug-induced seizures but also inter-ictal events.

METHODOLOGY

A total of 442 EEG traces from rats, dogs, minipigs and non-human primates were evaluated for spike frequency, amplitude and duration but also premonitory and post-ictal changes.

RESULTS

Most drug-induced seizure events were self-limiting. In all species, post-ictal EEG changes were observed over a period of a few minutes only after a seizure episode with resolution prior to clinical signs. Characteristic profiles were noted for individual animals but also with each drug (i.e. similar patterns noted for a given animal or specific to a drug). Most drug-induced seizures were noted at times of maximal plasma exposure but delayed seizure onset was noted in rare cases. Seizure onsets were associated with stimulation (e.g. handling or lights) in some cases as reported with non-drug related seizures.

CONCLUSION

Overall, this analysis reveals a rich diversity in EEG morphologies associated with drug-induced seizures with implications when selecting detection algorithms, EEG derivations or during manual morphology review.

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TOXICOLOGY SERVICES
- General toxicology in all species
- Special toxicology
  - Infusion
  - Inhalation
  - Dermal
  - Ocule
- Immunotoxicology
- Regenerative medicine
- Reproductive toxicology including minipigs and NHPs
- Carcinogenicity studies also in rasH2 and p53+/- mice
- Genetic toxicology: ICH compliant package
  - In vitro toxicology: BOCOP, h-CLAT, KaratinosSens™, DPRA, Photo 3T3-NR4, Epilink™, chicken eye test
  - Agrochemical / chemical / REACH
  - QSAR
  - Physico-chemical testing
  - Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
- Integrated safety pharmacology in toxicity studies
  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNE (FOB) and JET-EEG

MEDICAL DEVICE
- Biocompatibility testing
- Cardiovascular stents, electrophysiology and structural heart studies
- Long-bone defects and craniofacial/dental models
- Spinal fusion models
- Joint and cartilage repair models
- Regenerative medicine (growth factors, biomaterials, cell and gene therapy)

DMPK, BIOANALYSIS, BIOMARKERS
- IC and IADME studies in all species
- In vitro metabolic clearance, metabolite ID and profiling, DDI package (metabolism and transporters)
- Bioanalysis: LC-MS/MS, GC-MS/MS, LC-ICP/MS, LC-Radioscopy, ELISA, RIA
- Toxicogenomics, miRNA: Affymetrix™ accredited service provider, next generation sequencing (Illumina®)
- Immunology: 10-color flow cytometer, Lumines, Maso Scale

SPECIALIZED EXPERTISE
- Juvenile studies including minipigs
- Otoxicity in rats
- Fertility studies in rodents and NHPs
- Radiation safety and efficacy studies
- Tissue Cross Reactivity (TCR): human and animal tissue banks
- Gene therapy vector biodistribution via qPCR
- ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
- Lead optimization and predictive toxicology services: Leadscreen™

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