Seizure liabilities represent a major safety concern in drug development given potentially life-threatening consequences to patients. Numerous models are commonly used to assess pro- and anti-convulsive effects of drug candidates. Pentylenetetrazol infusion in rats is a model often used to evaluate seizure threshold. EEG, arterial pressure and EMG monitored simultaneously by telemetry represent a recognized methodology to assess pharmacological effects of test articles on the central nervous system of various species including rats, canines and non human primates. Telemetry in freely moving animals enable recording of high quality EEG with minimal artifacts compared with restrained recording.

Telemetry also allows for continuous video-EEG recording, hence capturing rare events (e.g. seizure or paroxysmal activity) with unpredictable onset. Video-EEG is the standard diagnostic method to assess seizure in human patients and this methodology is widely accepted as a preclinical tool to assess seizure liability. Supported by scientific literature, Beagle dogs are recognized to present a genetic predisposition to idiopathic epilepsy and regulatory agencies typically acknowledge the possible bias in predictive value of this breed to the human response. Interactions with regulatory agencies can be used to ensure the species and model selected are the most appropriate to assess the clinical risk.

Based on prior regulatory interactions, clinical hold for seizure liability noted in preclinical studies can be lifted with appropriately designed animal studies that aim to 1) characterize the nature of the CNS adverse effect in relevant species and 2) confirm systemic exposure at onset of the CNS adverse effect by test article plasma levels. Some programs will identify CNS adverse effects that are not seizure (e.g. vestibular syndrome) and represent a lower risk for the patient population. When last article induced seizures are confirmed, the studies will further aim to 3) identify precurser clinical signs that precede seizures and can be used during clinical studies to monitor for signs of neurotoxicity and halt human studies in an appropriate manner. 4) confirm that seizures are self-limiting and 5) confirm that seizure can be treated with commercially available anticonvulsive drug.

Materials and methods

The pentylenetetrazol (PTZ) infusion and video-EEG are commonly used non-clinical models to evaluate seizure liabilities. Rats received PTZ IV at a rate of 288 mg/kg/hr after pre-treatment with phenobarbital or yohimbine. The 1st myoclonus, 1st clonic convolution and 1st tonic convulsions were recorded. Cynomolgus monkeys and Beagle dogs implanted with EEG telemetry transmitters (Data Science International, TL192-0700-EEE) and three bipolar derivations (C3-O1, Cz-Oz and C4-O2) were used for drug-induced seizure assessments. Pre-ictal spectral changes were evaluated using baseline clinial signs and spectral bands (delta, theta, alpha, sigma, beta and gamma). Continuous monitoring of clinical signs was used to identify possible prodromal signs.

Results

Drug induced seizures typically lasted less than 1 minute in all species and presented expected prodromal and post-ictal signs (clinical signs and EEG). Diazepam, propofol or phencyclidine controlled drug induced seizures in non human primates and canines. Positive control drugs induced expected anti-convulsive and pro-convulsive effects in rats receiving a continuous IV infusion of PTZ (Figures 2 and 3). Power analysis identified similar pre-ictal spectral EEG changes in 58% of the animals. The remaining animals presented no remarkable pre-ictal spectral change (10%) or spectral changes that were unique and different from other animals (32%). Prodomal clinical signs often progressed in severity prior to seizure and included decreased physical activity, enhanced physiological tremors, hypersalivation, ataxia, emesis and myoclonus, generally in ascending order of severity. The current EEG analysis identified pre-ictal spectral changes which included an increase in power bands at frequencies above 4 Hz.

The dominant power band in cynomolgus (delta activity) differs from humans (alpha activity). Similar to dominant spectral frequencies, pre-ictal changes in cynomolgus appear to differ from humans in which an increase in delta components is mainly observed (Khammari et al., 2012). Abundant scientific literature confirms genetic predisposition to idiopathic epilepsy in Beagle dogs rendering this species of limited translational relevance to assess seizure liabilities in humans (Gredal et al., 2003; Morita et al., 1999; Montgomery & Lee 1983; Edmonds et al. 1979). It remains that seizure liability was evaluated in Beagle in some cases when required by regulatory agencies following observations in canine toxicology studies. Our historical data confirms the feasibility of video-EEG monitoring in Beagle dogs to evaluate seizure liability with PTZ (IV infusion at 100 mg/kg/hr) as a relevant positive control when appropriate.

Discussion & Conclusion

Our historical database and the current analysis confirm that the rat PTZ model can be useful to screen for seizure liabilities but rodents typically have lower translational relevance when compared with non-human primates. Beagle dogs present a greater sensitivity to seizure in a number of cases and are only used when required by regulatory agencies. Objectives of seizure liability studies commonly include:

- Confirmation that drug-induced seizures are self-limiting
- Measurement of plasma level at seizure onset
- Identification of prodromal clinical signs which can be monitored in clinical trials
- Confirmation that conventional drugs (e.g. diazepam) can successfully treat drug-induced seizures
- Confirmation of the No Observed Adverse Effect Level (NOAEL) by absence of paroxysmal EEG activity

Telemetered EEG monitoring in large animals can be used to achieve the goals listed above in drug candidate seizure liability evaluations and lift clinical hold as appropriate due to non-clinical toxicology studies. Our experience confirmed that the video-EEG model with telemetry was well accepted by regulatory agencies to evaluate seizure liability. When possible, review and discussion of the seizure liability, study protocol with the Agency provided valuable interactions towards an agreed study design, inclusion of comments from the Agency facilitated final regulatory review.

Reference


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