INTRODUCTION

Seizure liabilities represent a major safety concern in drug development given potentially life-threatening consequences to patients. EEG and EMG monitoring by telemetry is a recognized methodology to assess pharmacological effects of test articles on the central nervous system (CNS) of various species including rats, dogs and non human primates (NHPs). Continuous telemetry monitoring with synchronized video enables detection and characterization of neurological adverse events with unpredictable onset. Such models are useful to satisfy regulatory requirements for CNS safety testing but also to provide important safety data for clinicians prior to human trials.

MATERIALS AND METHODS

Sprague-Dawley rats, Beagle dogs and cynomolgus monkeys were implanted with EEG telemetry transmitters followed by at least 2 weeks of recovery (Rats: DSI, model CS0-PXT, dogs and monkeys: DSI, model D70-EEE). EEG derivations were based on the 10-20 system (Rats: Cz-Oz, dogs: Cz-O2, C4-O2 and EMG and monkeys: C3-O1, Cz-O2 and C4-O2 or F3-C3, Cz-Oz and EMG). Pre-ictal spectral changes were evaluated using baseline changes in power bands (delta, theta, alpha, sigma, beta and gamma). Continuous monitoring of clinical signs was used to identify possible prodromal signs.

RESULTS

The PTZ dose required to induce convulsion was 31.2, 35.6, 48.3 mg/kg, in Sprague-Dawley rats, Beagle dogs and cynomolgus monkeys, respectively. Prodromal 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 leading to ictus.

DISCUSSION AND CONCLUSIONS

Each drug development program needs to be treated on a case-by-case basis with science-driven decisions. The rat is often used when the seizure threshold needs to be assessed relative to a reference compound or during early screening. Beagle dogs represent an important model in seizure liabilities given the high comparability to humans (premonitory signs, spectral components, sleep cycles, etc.) (Authier et al.).

Objective of seizure liability studies commonly include:
- 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 activity.
- 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 activity.
- Our historical database and the current analysis confirm that the telemetered rats, Beagle dogs and cynomolgus monkeys can be used to achieve the above goals in drug candidate seizure liability evaluations.

REFERENCES

