INTRODUCTION

The EEG is an important tool for cardiovascular safety pharmacology, but it is not often used for CNS safety pharmacology purposes. With significant use of radiotelemetry technology to allow the recording of EEG from conscious, unrestrained dogs.

The EEG is a non-invasive tool that can be used to identify pathologic brain activity, in particular drug-induced paroxysmal activity. The use of the tool EEG may be especially useful in situations where results from cardiovascular and CNS safety tests in the same species are required or in the use of lower doses in combination with other animal or pharmaceutical manipulations.

MATERIAL & METHODS

Dogs were implanted with epidural electrodes positioned over the motor cortex and connected to a radiotelemetry EEG system. EEG was monitored continuously for 24 hours in order to exclude spontaneous paroxysmal activity. After substance administration, the EEG was recorded for at least 24 hours, with the first 12 hours being recorded on film. After completion of the recording, all EEG traces were analyzed off-line and visually inspected for aberrant activity. In order to validate the recordings, the convulsant pentylenetetrazole (PTZ) was used as a positive control. All EEG recordings were compared to either clear EEG effects and/or behavioral symptoms occurred. This typically occurred 25 minutes (range 15-30) after the start of the infusion. Then the infusion was stopped and the dogs allowed to recover until the next test substance administration. EEG recordings were performed either with a 2 x 1 mg/kg i.v. or 2 x 1 mg/kg i.m. dose. Because of the i.v. administration, the dogs had to be placed in a sling for the recording.

RESULTS

Figure 1a shows a 20 second EEG sequence of baseline recording prior to substance administration. The trace shows normal EEG activity of an awake dog.

Figure 1b shows a 20 second EEG sequence of the same dog asleep. Sleep spindles (marked between square brackets) must not be confused with paroxysmal activity.

Figure 2 shows a 20 second EEG sequence following a test substance administration. The substance induced paroxysmal spike-and-wave activity. The representative example shown lasted 8 seconds and had a frequency of about 4-5 Hz. It is to be noted that the paroxysmal activity observed with the test substance was not accompanied by any overt convulsive activity.

Figure 3 shows a 20 second EEG sequence during PTZ i.v. infusion. The sequence was recorded 10 minutes after the start of PTZ infusion. A sequence of paroxysmal EEG activity (marked between square brackets) followed by a sequence of normal EEG was observed. The activity consisted of spikes and wave trains with a frequency of about 4-5 Hz. The activity was accompanied by clear convulsions.

DISCUSSION & CONCLUSION

EEG is considered as a supplemental procedure in safety pharmacology. Although the rat is the commonly used species for EEG experiments, the presented data show that the dog EEG combined with a radiotelemetry system can be a useful alternative for special applications. In contrast to the rat, recordings from deep brain structures in dogs are not practicable.

In order to validate the EEG recordings, PTZ was used as a reference substance. Since convulsions were stopped with diazepam at early stages, dogs were not exposed to severe stress and it is unlikely to have caused measurable brain damage. There is no risk for brain damage following many repeated convulsions and especially following simple applications. Controlling seizures with diazepam thus allows to use dogs repeatedly which helps to make studies more cost-effective and ethically acceptable.

It is concluded that EEG recording in dogs is a valuable addition to CNS safety pharmacology procedures.

Acknowledgements: special thanks to Guillaume Peyon, Stefania Penloup and Sonia Rompion for their technical expertise.

Porsolt & Partners Pharmacology - All rights reserved

 Bastien Penloup and Sonia Rompion for their technical expertise.

EEG is considered as a supplemental procedure in safety pharmacology. Although the rat is the commonly used species for EEG experiments, the presented data show that the dog EEG combined with a radiotelemetry system can be a useful alternative for special applications. In contrast to the rat, recordings from deep brain structures in dogs are not practicable.

DISCUSSION & CONCLUSION

EEG is considered as a supplemental procedure in safety pharmacology. Although the rat is the commonly used species for EEG experiments, the presented data show that the dog EEG combined with a radiotelemetry system can be a useful alternative for special applications. In contrast to the rat, recordings from deep brain structures in dogs are not practicable.

In order to validate the EEG recordings, PTZ was used as a reference substance. Since convulsions were stopped with diazepam at early stages, dogs were not exposed to severe stress and it is unlikely to have caused measurable brain damage. There is no risk for brain damage following many repeated convulsions and especially following simple applications. Controlling seizures with diazepam thus allows to use dogs repeatedly which helps to make studies more cost-effective and ethically acceptable.

It is concluded that EEG recording in dogs is a valuable addition to CNS safety pharmacology procedures.

Acknowledgements: special thanks to Guillaume Peyon, Stefania Penloup and Sonia Rompion for their technical expertise.

Porsolt & Partners Pharmacology - All rights reserved

 Bastien Penloup and Sonia Rompion for their technical expertise.

EEG is considered as a supplemental procedure in safety pharmacology. Although the rat is the commonly used species for EEG experiments, the presented data show that the dog EEG combined with a radiotelemetry system can be a useful alternative for special applications. In contrast to the rat, recordings from deep brain structures in dogs are not practicable.

Porsolt & Partners Pharmacology - All rights reserved

 Bastien Penloup and Sonia Rompion for their technical expertise.

EEG is considered as a supplemental procedure in safety pharmacology. Although the rat is the commonly used species for EEG experiments, the presented data show that the dog EEG combined with a radiotelemetry system can be a useful alternative for special applications. In contrast to the rat, recordings from deep brain structures in dogs are not practicable.

Porsolt & Partners Pharmacology - All rights reserved

 Bastien Penloup and Sonia Rompion for their technical expertise.