

TITLE: Novel Epilepsy Studies in the Naturally Occurring Canine Model

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Background: Naturally occurring epilepsy is a common canine condition with a prevalence of 1-5%. Controlled studies can be performed with just IACUC approval and informed consent of the dog owner, and can provide data from a large animal translational model as a stepping-stone to human studies.

Methods: Our research group has just completed studies on the safety and pharmacokinetics of IM levetiracetam (LEV), and a randomized clinical trial (RCT) of IV levetiracetam in 19 dogs for the treatment of status epilepticus after diazepam had failed. In addition we have ongoing studies in dogs with naturally occurring epilepsy in which an intracranial EEG (iEEG) system has been implanted. Initial iEEG studies looked at detecting seizures and alerting caregivers to prolonged or repetitive seizures. In addition, we have ongoing iEEG studies aimed at reliable seizure prediction in conjunction with timely short-term intervention to prevent epileptic seizures before they occur in this canine model.

Results: IM LEV was well tolerated in normal dogs and plasma levels that were above or within the therapeutic range were achieved for at least 7 hours. These results then led to a phase 1 IM study in people. In the IV LEV RCT, the responder rate (defined as dogs with no further seizures after administration of the study medication) showed a trend toward superiority of levetiracetam compared to placebo (56% vs 10% responder rate; p=0.057). No serious adverse effects were attributable to LEV. For the iEEG seizure detection and caregiver alert studies, 4 dogs exhibited electrographically similar onset and progression characteristics of human complex partial seizures. Three prolonged or repetitive seizures occurred in 2 dogs. On each occasion, wireless alerts were sent to a staff veterinarian who confirmed the seizure activity via remote video-monitoring. A rescue medication protocol was then administered and the repetitive seizures were aborted in both dogs. In addition, our research partnership has just been awarded a NINDS U01 grant for \$7.5 million for iEEG studies in this translational canine model to continue work on epileptic seizure prediction with control.