RESEARCH/PROJECT NAME: Use of Pharmacokinetic and Pharmacodynamic Modeling and Simulation as an AED Development Tool

PRESENTER:
Lisa Coles, PhD
[1]Center for Orphan Drug Research
Experimental and Clinical Pharmacology
College of Pharmacy, University of Minnesota

Co-Authors: Ilo E. Leppik, MD [1,2], Edward E. Patterson, MVD, PhD [3], James C. Cloyd, PharmD[1]
[2] University of Minnesota College of Veterinary Medicine, University of Minnesota [3] UMP MINCEP Epilepsy Care, Minneapolis, MN

CURRENT STATUS/TIMING:
Ongoing

OVERALL GOAL:
Use pharmacokinetic and pharmacodynamics modeling and simulation as part of preclinical animal studies to optimize dosing for safety and efficacy trials.

PROJECT SUMMARY:
The development of new therapies for epilepsies is hindered by the limitations of translating from animals to humans. Pharmacokinetic (PK) modeling and simulation can be employed in the preclinical stage of research to decrease costs, accelerate development, and increase the likelihood of success of bringing new therapies to patients with epilepsy. For example, we are conducting PK studies in a small number of dogs in which modeling and simulation are used to determine dosing for randomized, blinded, placebo-controlled trials in canine status epilepticus (CSE). We have recently completed two pilot PK studies, one with fosphenytoin (FOS) and one with topiramate, to determine the intravenous loading dose needed for dogs to attain target drug concentrations. For each study, four dogs were used to characterize the pharmacokinetics. Blood samples were collected from which drug plasma concentrations were measured using HPLC-MS. Non-compartmental PK parameters were determined and compartmental PK modeling and simulations were used to select the dose for the clinical trial with a target goals. Based on the simulations, a dose of 15mg/kg of FOS was selected and used in the clinical trial of CSE. Using this approach, we attained targeted plasma phenytoin concentrations in 15/16 dogs randomized to the treatment arm. Treatment with FOS was statistically superior to placebo and the response rate was approximately the same as report in controlled trials in humans. As another example, we are using PK modeling and simulation to evaluate therapies for infantile spasms using mouse models. For this work, pharmacokinetic/pharmacodynamic models will be developed using single dose data and multiple dose regimens will be simulated in order to optimize dosing for long-term efficacy and safety studies. In summary, use of PK modeling and simulations can help determine safe and effective dosage regimens for subsequent animal clinical studies, which in turn can, inform design of human clinical studies.