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Canine Status Epilepticus: A Translational Platform for Human Therapeutic Trials

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Convulsive HSE affects an estimated 152,000 persons and causes 42,000 deaths each year in the USA (DeLorenzo, 2006). Treatment of human status epilepticus (HSE) is based on studies performed more than two decades ago using drugs developed 10 to 50 years or more before the studies. Successful treatment rates were only 67% with lorazepam and 44% with phenytoin (Treiman DM *et al.*, 1998). These drugs now form the basis of the international HSE treatment guidelines (Kalviainen, 2007). A major barrier to the development of new drugs for HSE is providing enough pre-clinical evidence of safety and efficacy to justify the of conduct human studies. Results from studies performed in small animals with experimental SE may not be sufficient to convince trial sponsors to proceed with development of drugs in humans. Further, the available drugs for HSE were initially developed for chronic treatment of epilepsy, and only used for HSE after intravenous preparations became available. The mechanisms driving HSE may differ from the triggers of isolated seizures, and the best drugs for chronic epilepsy may not be the best choices to abort HSE. During the 2007 London Colloquium on SE, it became clear that many agents tested in small animal SE models had the potentially significant advantages over current agents. One of many of these is NS 1209, which is very effective in a model of status epilepticus but is not being developed for human use (Pitkanen A *et al.*, 2007). However, many of these are not candidates for chronic epilepsy therapy, thus they will not proceed to clinical development. This led us to consider using CSE as a translational platform.

The small animal (rodent) SE models have two shortcomings, which make it difficult to apply results to treating HSE. First, none of the models have counterparts in the human condition; they are usually induced by chemicals or electrical kindling (Sloviter RS *et al.*, 2007). Secondly, scaling doses from rodents to humans involves a body size difference of more than 4000 fold and scaling is not linear (Leppik IE, 1998). This enormous difference may lead to substantial errors in selecting doses for humans. Clearly a test species having

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naturally occurring SE similar to humans and closer in terms of pharmacokinetic characteristics would be very useful.

Canine Status Epilepticus (CSE)

Naturally occurring epilepsy in dogs and CSE has many striking similarities to the human condition. The clinical manifestations of seizures in dogs are very similar to those observed in humans. Veterinarians have observed simple partial, complex partial, and tonic-clonic seizures in their population (Licht BG *et al.*, 2002a; Licht BG *et al.*, 2002b). Also, electroencephalographic studies have demonstrated that interictal and ictal patterns observed in dogs are similar to those seen in humans (Berendt M *et al.*, 1999). Naturally occurring CSE is one of the more common emergency conditions treated at veterinary hospitals (Platt SR & Hagg M, 2002). Approximately 59% of dogs with epilepsy have one or more episodes of CSE during their lifetime, and those with CSE had a mean life span of only 8.3 years compared to 11.3 years for those with epilepsy but no CSE (Saito M *et al.*, 2001; Platt SR & Hagg M, 2002). Treatment of 156 cases of CSE required continuous diazepam infusion (66.8%) or constant phenobarbital infusions (18.7%) for a mean of 22 hrs. with 25.3% not surviving (Bateman SW & JM., 1999).

Evaluating drugs for SE in dogs has three advantages: 1) canine SE studies could provide proof of principle evidence for efficacy and more readily assess adverse effects such as cardiac arrhythmias, hypotension and behavioral changes;; 2) distribution volumes in dogs are similar to those in humans; this and the fact that dogs are closer to humans in size provide much better information regarding the effective dose and target plasma concentrations for humans; and 3) because FDA approved treatments for canine SE are not available, approval for a placebo-controlled study is possible. Use of naturally occurring CSE has many cost advantages. Studies can be performed with many fewer subjects than needed for human subjects and the cost per subject is much lower. Additionally, finding effective treatments for dogs will also benefit the veterinary community.

Pilot study

A pilot study of levetiracetam (LEV) in CSE was able to show a strong statistical trend for efficacy (Patterson EE & Hardy BT). It was performed as a randomized, placebo-controlled, double-masked study with dogs that presented to the University of Minnesota Veterinary Medical Center. Dogs presenting with CSE or repetitive seizures were initially treated with IV diazepam (0.5–1mg/kg) or rectal diazepam (1–2mg/kg).

They were enrolled and treated if they had another seizure while under observation. The first 10 dogs received 30mg/kg of LEV or an equivalent volume of 0.9% saline. Since no adverse effects were seen at planned interim analysis of the first 10 patients, the dose was escalated to 60mg/kg LEV or an equivalent volume of 0.9% saline for the last 9 dogs. The solution was administered IV as a slow bolus over 5 minutes. The most common breeds were Boston Terrier and Golden Retriever, (3 each) and Labrador Retrievers (2 each). There were 11 other breeds with one each in the study. Idiopathic epilepsy was the most common etiology of seizures in both groups. Response rate was defined as having no further seizures after administration of LEV or placebo. In the LEV group 5/9 (56%) of dogs were classified as responders, compared to only 1/10 (10%) in the placebo group ($p = 0.057$).

Current Study

Demonstrating that CSE studies could be done successfully was instrumental in obtaining an NIH grant for a proof of principle study to further explore the usefulness of this new approach. The proposal is to treat dogs with established CSE with loading doses of

fosphenytoin (FOS) designed to attain phenytoin concentrations similar to those attained in humans following loading doses of 18 mg/kg (Cranford RE *et al.*, 1978). FOS was developed to avoid the toxic effects IV PHT (Leppik IE *et al.*, 1990). FOS is now widely prescribed for HSE and will be used in this study. The trial is a randomized, double-blind, placebo-controlled investigation of FOS vs. saline. Validation of the canine platform will be based on: 1) statistical superiority of the FOS (50% response) vs. placebo (10% response), powering the study for a 40% difference; and 2) a response rate of approximately 50% for FOS, similar to that observed for PHT in HSE trials. The study involves two phases: phase 1 is a pharmacokinetic trial in 4 dogs to determine the dose needed to attain desired unbound plasma PHT concentrations and a second phase designed to evaluate FOS efficacy and safety involving 60 canine subjects. Phase 1 has been completed (Craft EM *et al.*, 2011) and results analyzed by the Center for Orphan Drug Research laboratory, University of Minnesota (Drs. James Cloyd and Lisa Coles). An initial test dose of 25mg/kg produced unbound phenytoin concentrations in the 3.0–4.5ug/ml range 30 minutes following dosing (4.6–6.3 ug/mL 15 minutes following dosing) (Figure 1). These unbound levels were higher than expected and were associated with ataxia and, in one, vomiting. A dose of 15 mg/kg was tolerated, and because of lower protein binding in dogs, produced unbound phenytoin concentrations (2.0–2.5 ug/ml) that are in the range observed when treating HSE even though the total levels were in the 12–13 ug/mL range, lower than in humans following 18 mg/kg (Table 1, Figure 1). Approximately 80% of FOS was protein-bound 15 minutes following dosing, compared to ~90–95% which has been reported for humans. Furthermore, ~80% of fosphenytoin was converted to phenytoin by 30 minutes suggesting rapid metabolism similar to that observed in humans. Additional pharmacokinetic parameters for total phenytoin determined using non-compartmental analysis are summarized in Table 1. Pharmacokinetic models were developed to predict optimal doses for the second phase of the study.

The second phase is being conducted at 3 veterinary hospitals: University of Minnesota Veterinary Medical Center (Dr. Edward Patterson); The Chicago Veterinary Emergency and Specialty Center, (Dr. Michael Podell); and The University of Pennsylvania Matthew J. Ryan Veterinary Hospital (Dr. Charles H. Vite).

Validation of the platform will be based on: 1) statistical superiority of the FOS (50% response) vs. placebo (10% response), powering the study for a 40% difference; and 2) a response rate of approximately 50% for FOS, similar to that observed for PHT in HSE trials. If we are able to demonstrate the validity of CSE as a platform for testing drugs discovered in animal models, a process of therapeutic development can be initiated that will enable future testing.

Future plans

If we can demonstrate that CSE is a valid translational platform for HSE, we will initiate a process of therapeutic development to make drugs discovered in the laboratory available for the treatment of HSE. If we are able to demonstrate the validity of CSE as a platform for testing drugs discovered in animal models, a process of therapeutic development can be initiated that will enable: 1) establishment of a national network of veterinary emergency care departments similar to the human Neurological Emergencies Treatment Trials (NETT) system; 2) use the CNETT to test specific novel agents, and 3) make the CNETT available to basic scientists and industry to test new compounds for HSE. The results from 2 and 3 may be used to inform IND applications and support for treatment of HSE.

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Figure 1.

A) FC713 and FC 14 received 15 mg/kg of phenytoin equivalent FOS intravenously over 5 minutes. This dose was well tolerated and produced unbound phenytoin concentrations similar to those observed in humans after 18 mg/kg of phenytoin intravenously. **B)** FC 7 and 17 received 25 mg/kg of phenytoin equivalent FOS over X minutes? but had vomiting and ataxia, with levels in the human toxic range.

Table 1

Pharmacokinetic parameters for total (unbound + bound) phenytoin following a single bolus IV dose of fosphenytoin to dogs (non-compartmental analysis)

Phenytoin Equivalent Dose	15 mg/kg		25 mg/kg	
	10FC713	10FC14	10FC7	10FC17
Dose (mg/kg)	14.8	15.0	24.8	24.3
$t_{1/2}$ (hr)	3.51	2.78	3.62	3.22
C _{max} (5 min) (ug/mL)	12.2	13.9	39.0	26.2
C (30 min) (ug/mL)	10.8	11.3	26.6	21.0
C (1 hr) (ug/mL)	9.67	10.2	22.3	18.6
C (2hr) (ug/mL)	8.35	7.52	19.8	15.9
AUC (0–12 hr) (ug*min/mL)	3580	2890	8970	7070
AUC (0-inf) (ug*min/mL)	3940	3060	9980	7760
V _d (L/kg)	1.14	1.18	0.78	0.87
CL (L/hr/kg)	0.23	0.29	0.15	0.19