Abstract

The mainstay of comparative research for epilepsy has been rodent models of induced epilepsy. This rodent basic science is essential, but it does not always translate to similar results in people, likely because induced epilepsy is not always similar enough to naturally occurring epilepsy. A good large animal, intermediate model would be very helpful to potentially bridge this translational gap. Epilepsy is the most common medical neurologic disease of dogs. It has been proposed since the 1970s that dogs with naturally occurring epilepsy could potentially be used as a comparative model for people of the underlying basis and therapy of epilepsy. There have been sporadic studies in the decades since then, with a relative surge in the last 10 years. These canine studies in the areas of genetics, drug therapy, dietary therapy, electroencephalogram research, and devices for epilepsy show proof of concept that canine epilepsy can be a very good model for comparative research for many, but not all, facets of epilepsy. Results of research in canine epilepsy can and have benefited the improvement of treatment for both people and dogs.

Key Words: canine; device; drugs; EEG; epilepsy; model; seizure

Background: Canine and Human Epilepsy and Research Models

Naturally occurring epilepsy is one of the most common reasons a dog owner brings their pet to a veterinary clinic because it is the most common medical neurologic diseases in dogs (Podell et al. 1995). The clinical manifestation of seizures in dogs is very similar to those observed in humans; veterinarians have observed, for example, focal (with or without impairment or alteration of consciousness) and generalized tonic-clonic seizures in dogs (Leppik et al. 2009). Also, electroencephalograph (EEG) studies have demonstrated that inter-ictal and ictal patterns observed in dogs have similarities to those seen in humans (Berendt et al. 1999). In addition subdural electrode recordings also show EEG patterns very similar to those recorded from humans (Davis et al. 2012). Canine epilepsy has been proposed as a model for epilepsy studies to translate to human epilepsy since the 1970s (Frey et al. 1979; Hegreberg and Padgett 1976). Recently there has been renewed interest and analysis of the possibility of more fully using the canine model for translational research (Leppik et al. 2011; Potschka et al. 2013).

Varying definitions for the terms “epileptic seizure” and “epilepsy” have been used. Recently, consensus definitions for epilepsy in people have been proposed by the International League Against Epilepsy (ILAE) (Fisher et al. 2005). In this definition, epileptic seizure is defined as the transient occurrence of signs due to abnormal excessive or synchronous neuronal activity in the brain that is characterized by “an enduring predisposition to generate epileptic seizures.” This definition of epilepsy requires the occurrence of at least one epileptic seizure. Other classification systems have, in the past, indicated that the patient must experience at least two (therefore, recurrent) seizures over time to be classified as having epilepsy (Blume et al. 2001). Recently it has been proposed to try to fit definitions for dogs (Mariani 2013) with the ILAE definitions (Fisher et al. 2005).

Canine epilepsy can result from structural, metabolic, genetic, or unknown causes. Metabolic (extracranial) causes include metabolic abnormalities (e.g., hypoglycemia) and chemical toxicities (e.g., lead poisoning). Structural (intracranial) causes include brain neoplasia, infection, inflammation, or head injury. Primary causes of epilepsy in which no identifiable structural cause can be detected are now termed genetic epilepsy (previously termed idiopathic or primary epilepsy) (Mariani 2013).

The prevalence of epilepsy in humans is reported to be in the range of 4 to 10 per 1000 in most study settings or 1% of the general population (Sander 2003) with an estimated 3 million epileptic people in the United States. The prevalence in dogs was estimated to be at least 0.55% in a hospital referral population (Loscher et al. 1985), with some estimates in the general dog population of up to 5% (Podell et al. 1995). An extrapolation of the midrange of these figures would result in an estimate of 2.1 million epileptic dogs in the United States alone. Generalized seizures and focal seizures occur in both species. A generalized seizure is often defined as a seizure...
in which the first clinical changes indicate the initial involvement of both cerebral hemispheres, and a focal (partial) seizure is often defined as a seizure that originates within neuronal networks limited to one hemisphere (Mariani 2013).

Although canine epilepsy could be considered a model of epilepsy, the disorder in dogs is, in fact, actual epilepsy by definition and has many clinical (Chandler 2006), electrographic (Berendt et al. 1999), and pharmacologic (Volk et al. 2008) similarities to human epilepsy. For instance, it has been recently shown by intracranial EEG recordings that dogs with naturally occurring epilepsy can have focal onset seizures with secondary generalization that are indistinguishable from EEGs in people (Davis et al. 2012). Many drugs that work well in human epilepsy also work well in canine epilepsy if similar serum levels can be maintained. Examples include phenobarbital, felbamate, levetiracetam, and zonisamide. Some drugs, however, such as phenytoin and valproate do no work well in dogs (Thomas 2010) because of a shorter half-life in dogs. The results of studies in dogs with naturally occurring epilepsy can be potentially applied to people and vice versa, and therefore, there are bidirectional benefits between studies of human and canine epilepsy.

The four major therapeutic modalities for the treatment of epilepsy in people are (1) antiepileptic drugs (AEDs), (2) surgery, (3) diet, and (4) devices/neuromodulation. Drugs are most often the initial therapy of choice (Podell 2013), and the other three modalities are usually reserved for refractory epilepsy in which a patient (human or dog) is still having frequent seizures even though they have achieved therapeutic blood levels of two or more AEDs (Privitera 2011). There are no published studies of surgery for primary epilepsy in dogs. There have been published studies of drug therapy, diet therapy, and devices for in canine epilepsy.

Areas in which canine epilepsy has already been used or could soon be a translational model include genetics, AED therapy, EEG research, dietary therapy, and devices for refractory epilepsy. This review will summarize historical and recent canine epilepsy research in these five areas.

**Genetic Causes**

It is estimated that up to 70% of recurrent seizure disorders in dogs and 10% in people are genetically related (Ekenstedt et al. 2012). Within genetically related epilepsies are two types: (1) progressive epilepsies, which are syndromic, with other signs and symptoms that invariably worsen over time; and (2) genetic (idiopathic) epilepsies, in which there are not any other signs or symptoms beyond seizures. Genetic (idiopathic) epilepsy is defined as recurrent seizures without a detectable underlying cause and is presumed to be genetically associated. In the ILAE classification system, (human) genetic epilepsy is always considered a generalized seizure disorder, and partial seizures without a known cause are termed cryptogenic (Mariani 2013) because post mortem focal lesions can sometimes be identified. In the veterinary specialty community, some clinicians use the term “idiopathic epilepsy” for all seizure disorders with an unknown cause that are presumed to be genetically related, whereas other veterinary clinicians do differentiate between idiopathic and cryptogenic epilepsies. Recently, it has been proposed that genetic epilepsy replace the term idiopathic or primary epilepsy in dogs (Mariani 2013). It has been advocated that the domesticated dog is uniquely suited as a model for understanding the genetics of complex diseases such as cancer, diabetes, and epilepsy because of the inbreeding needed to produce purebred dogs (Karlsson and Lindblad-Toh 2008).

**Canine Models of Progressive Epilepsy**

There are a number of progressive epilepsy disorders for which canine correlates have been found, including Lafora disease and neuronal ceroid-lipofuscinoses. Canine progressive epilepsies were suggested as a naturally occurring model as early as 1976 (Hegreberg and Padgett 1976). To date, nine genes (EPM2B, CLN8, CLN5, CTSD, TPP1, PPT1, ARSG, CLN6, ATP13A2) for progressive epilepsies have been identified (Ekenstedt and Oberbauer 2013), and most of these mutations in dogs have mutations in the same gene in people causing the same disorder. In the future there is hope that experimental gene therapy in dogs might translate to a viable therapy in people.

**Canine Models of Genetic and Unknown (Cryptogenic) Epilepsy**

Genetic and unknown epilepsies in dogs are very common (Ekenstedt et al. 2012). Although there has not yet been a definitive mutation first identified in dogs for genetic epilepsy that then was later confirmed to also cause epilepsy in people, with continued intensive research into the genetics of canine epilepsy this will likely happen in the near future. Recently a locus for a gene in polygenic genetic epilepsy in Belgian Terveren dogs was identified (Seppala et al. 2012). Even though there has not yet been a strong breakthrough in definitive genes of canine genetic or epilepsy, dogs with these forms of epilepsy have very similar clinical signs, disease courses, and responses to therapy as people, and therefore dogs are a good model for the underlying genetics the therapy of genetic and unknown epilepsy.

**Canine Model of Dietary Therapy**

The ketogenic diet is a successful therapy for some people (especially children) with epilepsy that is refractory to two or more AEDs (Nei et al. 2014). A randomized clinical trial (RCT) with a ketogenic diet developed for dogs, however, was not successful. Dogs did have a statistically significant increase in serum ketones on the diet, but this increase was fivefold less than the increase obtained for people because of major differences in fat and liver metabolism in dogs (Patterson et al. 2005). There are some differences in specific...
subssets of metabolism in the dog model that results in the dog not always being a good model if simulating the effects of fasting is involved because dogs can fast for prolonged periods of time without becoming significantly ketotic (de Bruijne and van den Brom 1986), which is not the case for people (Dhamija et al. 2013). Despite this shortcoming, other diets with mechanisms that are not related to ketosis might potentially work for dogs.

Model of EEG and Medical Devices

To the author’s knowledge, the first study of a device in the canine model of naturally occurring epilepsy was with the vagal stimulator (Muñana et al. 2002). The response of dogs to treatment with the device in a controlled study was very similar to the results of studies in people with the same exact device, although it was only a single study in a limited number of dogs. In the canine study there was a decrease in mean seizure frequency of 34.4%, which is fairly close to the mean decrease of 42.8% reported in a meta-analysis of vagal stimulation for people (Connor et al. 2012). This is another example where dogs respond very similarly as people to specific treatments for epilepsy.

Additionally, in the past few years EEG research in dogs with intracranial devices has shown that dogs have very similar to identical EEG patterns to people. In continuous intracranial EEG (iEEG) recordings, it was shown that dogs often have focal epilepsy with secondary generalization (Davis et al. 2012). The senior author of this project has indicated that the EEGs from these recordings were discussed in Mayo Clinic EEG rounds without knowledge that the EEGs were from dogs, and other Mayo neurologists were fascinated that the recordings were indistinguishable from human EEG recordings (G. Worrell, Mayo Clinic, personal communication, 2012). This iEEG device is being developed for seizure detection and prediction in people, and Mayo Clinic researchers, along with our group and human and veterinary neurologists at the University of Pennsylvania recently published that this iEEG device is an effective seizure detection and caregiver alert device (Coles et al. 2013) and also is better than a chance predictor for seizure prediction minutes to hours before a seizure occurs (Howbert et al. 2014). The exact same device has been tested in 15 people in Australia with promising prediction results in a subset of the patients (Cook et al. 2013).

Recently, a study was published showing that depth electrodes for EEG could safely be implanted in normal dogs (Long et al. 2014), and there are plans to study this technology and other devices in dogs with epilepsy (M. Cook, University of Melbourne, personal communication, 2013). The simultaneous testing of medical devices in dog and people with similar results is further support that the dog is an excellent comparative naturally occurring model for many facets of epilepsy. The size of the dog brain is also an advantage because in many of these device studies the exact same device was used in dogs and people. In this bidirectional research, there are potential benefits for the therapy of both human and canine epilepsy. With successful canine studies of subdural and depth electrodes, it is likely that neuromodulation in the canine model will be studied in detail in the next few years.

There are still some limitations to EEG studies in dogs. It is still difficult to routinely perform ambulatory scalp EEGs in canine patients because of the difficulty of getting dogs to be still for hours without sedation because of and muscle artifact (Berendt et al. 1999). iEEG devices are quite invasive for people and dogs, but this author has hope for less invasive EEG monitoring devices being developed soon for both species.

Model of AED

Chronic Drug Therapy

Phenobarbital (Thomas 2010), levetiracetam (LEV) (Volk et al. 2008), and zonisamide (Dewey et al. 2004) are frequently used for dogs with epilepsy (and all are three are used in people). LEV was recently evaluated in an RCT in dogs for add-on therapy (Muñana et al. 2012). A novel compound, ELB138 (imipetoin), was tested for initial monotherapy in dogs with chemically induced seizures and also in a controlled clinical trial in client-owned dogs (Loscher et al. 2004) and has just been approved for use in dogs in Europe (Rundfeldt and Loscher 2014). Imepitoin is a partial benzodiazepam agonist, and these results in dogs may reactiviate interest in it or similar drugs being developed for people.

On a few other occasions, an induced model of epilepsy has been used with normal research dogs (Territo et al. 2007), but this is uncommonly done, and it is generally logistically difficult to get the number of dogs needed for statistical significance in the induced canine model.

Based on the aforementioned controlled AED studies in naturally occurring canine epilepsy, there is potential in the future to try newly developed compounds from rodent models in dogs before committing to large-scale US Food and Drug Administration trials in people for drug approval.

In RCTs, dogs are also a model for some of the placebo and clinical trial effects of controlled studies (Muñana et al. 2012). There are, however, some potential limitations of using dogs with naturally occurring seizures in translational studies such as the subjectivity of owner diaries of seizures variability of seizures in dogs versus induced rodent models (Potschka et al. 2013). In addition, some AEDs have shorter half-lives in dogs than in people (Loscher et al. 1985), and therefore it is sometimes hard to maintain steady plasma levels in dogs. In addition, a small subset of AEDs approved for people, such as lamotrigine and vigabatrin, are differently metabolized in dogs and have cardioxic (Lamictal [lamotrigine] package insert) and potentially neurotoxic (Gibson et al. 1990) byproducts, respectively, in dogs, but not in people. Despite these limitations, there is still promise in using client-owned dogs in drug studies of novel drugs because of the similarities in epilepsy between dogs and humans and because of dog owners’ willingness to often try
experimental treatments for refractory epilepsy when they are the point of possibly considering euthanasia.

### Acute Therapy for Seizure Emergencies

Dogs and people with epilepsy can have life-threatening seizures episodes, termed status epilepticus (SE), in which there is a seizure lasting more than 5 minutes or two or more seizures without recovery in between (Mariani 2013). When an intravenous formulation of the AED LEV was approved for people in 2006 for bridge therapy when a patient is unable to take oral medications, it was clear that it would soon be tried off-label for human SE. Additionally, for nursing home or ambulance treatment of SE or frequent seizures, intramuscular administration can be instituted much more quickly than an intravenous AED, which requires first getting an intravenous line running. Consequently, there might be potential for intramuscular use of LEV in people and dogs.

In 2008 our multidisciplinary group (veterinarians, [human] neurologists, and pharmacologists) published the results of intravenous and intramuscular pharmacokinetics of LEV in six normal dogs (Patterson et al. 2008) as a step to result in intramuscular phase 1 studies in people and intravenous studies in naturally occurring SE in dogs. Within a few years, we then published the results of the phase 1 trial of intramuscular LEV in healthy human volunteers (Leppik et al. 2010). The pharmacokinetic and safety results of intramuscular LEV in people were very similar to those in the dogs. Next, we published the results of an RCT in client-owned dogs with convulsive SE and found that intravenous LEV for SE and acute repetitive seizures was safe and potentially effective (Hardy et al. 2012). The results we found in the naturally occurring dog model were similar to those found in open-label studies in people, but the advantage was that in dogs it is easier to do RCT for emergency therapy because owners can consent to enroll their dog and, although institutional animal use and care committee approval is needed, US Food and Drug Administration approval is not needed for canine studies unless the drug is being developed for approval in dogs. Although this controlled intravenous LEV data in dogs was useful, intravenous LEV has not yet been well proven in a controlled trial in people. To further validate this canine translational model (Leppik et al. 2011), we have just completed an RCT for fosphenytoin (FOS) for SE in 32 dogs refractory to benzodiazepams coming into our veterinary hospital and three other veterinary centers (Patterson et al. 2013). Phenytoin/FOS is currently the recommended second-line agent in people with SE (Brophy et al. 2012). FOS is an intravenous prodrug of phenytoin. In the clinical trial in dogs, a statistically significant FOS response rate of 59% (Patterson 2013) was very similar to the veterans administration cooperative study RCT where there was a 55% response rate for phenytoin (Treiman et al. 1998). Full results of this FOS study in dogs are in preparation.

The similar FOS response rate in dogs for a well-established therapy in people is strong proof of concept that the dog model of SE is a valid translational platform in which RCTs with potential statistical significance can be performed in a relatively low number of canine clinical patients with naturally occurring epilepsy. Our multidisciplinary group next plans to test three novel compounds for SE in the dog model that have shown promise in induced rodent models of SE but would be unlikely to be tested soon in trials for people because of financial and logistical issues. If any of these new drugs for SE are effective in the large animal dog model this would likely result in a company having better incentive to bring the compound to development for human testing.

There are some inherent limitations in the canine model of SE, the most prominent being that EEGs are not yet routinely performed in canine intensive care units. Nonconvulsive SE could then be missed in dogs. Convulsive SE is very obvious in both canine and human patients in the hospital and home setting, and therefore the dog is a very strong model for convulsive SE. With the EEG advances in canine epilepsy in the past few years, EEGs may become more routine in the coming years in veterinary intensive care units, and when that occurs, the dog model could also be very good for nonconvulsive SE.

### Conclusions

It has been suggested since the 1970s that the canine model of epilepsy could be a useful comparative model. In the decade since then, there have been a very limited number of comparative studies of dog seizures in induced models, and recently a number of well designed studies of naturally occurring epilepsy in dogs. Some of the advantages of the naturally occurring canine model include the following: (1) disease surveillance in dogs is second only to that of people; (2) inbreeding in purebred dog breeds often makes the genetics easier to determine; (3) drug studies can be done at a lower cost than in people without the need for regulatory approval; and (4) full-sized epilepsy device prototypes can be used in dogs.

With a relative surge of proof-of-concept studies of naturally occurring epilepsy in the dog in the past 10 years, this useful model is now gaining traction. Dog owners are willing to sometimes try higher risk therapies if they are on the edge of euthanizing the dog because of poor seizure control. With the high prevalence of epilepsy in client-owned dogs, the results of canine comparative studies are not only of potential translational benefit for people but often also directly help improve the treatment of canine epilepsy. The canine translational model of epilepsy may well prove to be an excellent intermediate step for confirming basic research successes in the induced rodent models just before initiating human studies.

### References


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