Beyond Phenobarbital: New Ways to Stop Seizures

Natasha J. Olby, Vet MB, PhD, MRCVS, Diplomate, ACVIM (Neurology)
College of Veterinary Medicine
North Carolina State University
Raleigh, North Carolina

For many years, medical therapy of epilepsy in dogs, and to a lesser extent in cats, has centered on phenobarbital and potassium bromide. Both of these drugs are active at the $GABA_A$ receptor, activation of which causes hyperpolarization of neurons, thus reducing seizure frequency. These drugs are extremely effective—approximately 75% of dogs with primary epilepsy can be controlled by phenobarbital alone (1). Adding potassium bromide to phenobarbital will control a large percentage of dogs that have epilepsy refractory to phenobarbital alone (2). However, both drugs are limited by adverse side effects that, particularly in the case of phenobarbital, can be devastating. These side effects include polyuria/polydipsia, polyphagia, hepatotoxicity, bone marrow dyscrasias, and sedation. Potassium bromide is less likely to cause fatal complications, although it has been linked to pancreatitis in dogs and airway disease in cats. However, it commonly causes polyuria/polydipsia, polyphagia, and hindlimb weakness, and the sedative effects can be pronounced in some dogs. There has long been a need for antiepileptic drugs that are effective, safe, affordable, and practical in terms of dosing frequency. In the past 10 years, several drugs have emerged that are effective in humans, but cost and, in some cases, dosing frequency have rendered many of them impractical. As a result, they tend only to be used as a third line of drugs in animals with refractory epilepsy. With the passage of time, the emergence of generic drugs has brought some of these drugs into reach for most pet owners. This paper will review the most appropriate diagnostic approach to a dog with new onset of seizures and discuss these drugs in terms of both maintenance and emergency use.

Diagnostic Approach

New onset of seizures in a pet is always challenging and upsetting for an owner, and should be considered a serious medical problem that deserves a full diagnostic workup. The extent of the workup is determined by signalment, history, clinical signs, and the owners' desires. An accurate diagnosis is always the key to effective treatment. Seizures are a unique disorder because the veterinarian must often recommend a diagnostic workup and course of therapy without ever seeing the presenting sign, although the advent of smart phones has started to change this problem. Clearly, a precise history of the event itself should be obtained. Phenomena associated with seizures include a preictal period of changed behavior, loss or change of consciousness, increased muscle tone (could be in flexion or extension), autonomic signs, and a postictal period (3). Seizures occur primarily in resting, quiet dogs and usually involve the face, lips, and tongue due to their large representation in the motor and sensory cortex. On physical examination, it is important to identify any systemic abnormalities that may be significant, and the physical examination should include a fundic examination and blood pressure measurement. A neurologic examination is performed to identify focal signs that may indicate an underlying brain lesion, but it should be noted that a neurologic examination in the immediate postictal period can be misleading and should be repeated later if not normal. A full diagnostic workup starts by ruling out systemic or metabolic problems with routine bloodwork; urinalysis; additional endocrine testing; measurement of infectious disease titers; and liver

evaluation, if indicated. In older animals, routine thoracic radiographs should always be obtained, and initial physical examination and bloodwork may suggest a need for additional imaging (e.g., ultrasonography) of the abdomen. If no cause is identified, the next step is to perform advanced imaging of the brain combined with cerebrospinal fluid (CSF) analysis. However, the advanced imaging and CSF analysis may not always be critical. For example, in dogs with new onset of seizures at 1 to 5 years of age, no other health problems, no neurologic deficits between seizures, and of a breed known to have primary (idiopathic, presumed to be genetic) epilepsy, a routine systemic screen is all that is necessary. Advanced imaging is strongly recommended in dogs older than 6 years with new onset of seizures, in dogs with neurologic deficits between seizures, and in very young dogs. Both necrotizing encephalitis and granulomatous meningoencephalitis present in the 1- to 5-year age range in small breeds, such as Yorkshire terriers, Maltese terriers, pugs, and Chihuahuas (4). It is important to be aware of these important differential diagnoses when advising owners on the extent of workup in these breeds. If advanced imaging is not performed, owners should be given a list of neurologic signs to watch for that would increase the necessity of a full diagnostic workup.

Therapy

As noted, in the past the drug of choice when starting therapy was phenobarbital, in recognition of its known efficacy. Literature on phenobarbital and on potassium bromide is abundant (reference 3 contains a full review); this presentation will focus on newer drugs that are used with increasing frequency—zonisamide and levetiracetam. Both of these drugs can be used as the primary agent for treating epilepsy, bearing in mind that efficacy in this role has not yet been confirmed. They are both also commonly used in refractory epilepsy.

Zonisamide (Zonegran)

Zonisamide is a sulfonamide derivative that was first introduced in Japan in 1989. It has been licensed in the United States since 2000 but generic forms emerged more recently. The mechanism of action is not clearly defined. It is known to block excitatory sodium and calcium channels, has been proposed to be a carbonic anhydrase inhibitor (although this is not believed to be an important mechanism of seizure control), and to influence neurotransmitter synthesis and degradation. It is metabolized by the liver (not through cytochrome P450) and has a reasonably long half-life of 18 to 28 hours and thus can be administered twice daily to dogs. Canine studies in Japan have evaluated the dose rates needed to achieve blood levels known to be therapeutic in humans and have shown that 5 mg/kg twice a day is an appropriate starting dose for animals not on phenobarbital; a dose of 10 mg/kg twice a day is needed if they are on phenobarbital (5). The dose can be escalated safely: In a chronic toxicity study in dogs, doses as high as 75 mg/kg/day were administered for a year with only minor effects on appetite and weight (6). Side effects noted in canine clinical patients that were concurrently being treated with additional antiepileptic drugs include ataxia (responsive to dose reductions), lethargy, and vomiting. We recently encountered a case that appeared to develop idiosyncratic hepatotoxicity that resolved with discontinuation of the drug (7). There are two studies of the clinical efficacy of zonisamide as an add-on agent in refractory canine epilepsy (8,9), and both showed promising responses with reductions of seizures in 58% and 82% of dogs. However, neither study was controlled and both involved relatively low numbers of pharmacoresistant dogs. It is therefore difficult to draw conclusions for clinical decision-making apart from

confirming zonisamide's safety that, in addition to its affordability and the practicality of twice-daily dosing, now makes it a viable first choice for dogs with primary epilepsy. Although no data are available on its effectiveness as a single agent, they are likely to appear in the next couple of years. Reference blood levels have been taken from the human literature and are stated as 10 to 40 µg/ml; blood levels can be measured at the pharmacology laboratory at Auburn University College of Veterinary Medicine.

The pharmacokinetics and toxicity of zonisamide have also been evaluated in cats, and although the drug seems to be safe, doses cannot be escalated in the same way as in dogs: Approximately half of the cats receiving a dosage of 20 mg/kg/day became lethargic and ataxic and showed such gastrointestinal signs as anorexia, vomiting, and diarrhea. The half-life is 33 hours, so once-daily dosing at 5 to 10 mg/kg is recommended (10).

Levetiracetam (Keppra)

Levetiracetam has gained popularity since its approval for use in humans in 1999 due to its remarkable safety. It is believed to exert its effect by binding to the synaptic protein, SV2A, thus inhibiting excitatory neurotransmitter release. It is primarily excreted renally although there is minimal hepatic metabolism, making it ideal for any animal with compromised hepatic function. Its half-life in dogs is short—just 3.5 to 6 hours—and doses of 20 mg/kg three times a day will achieve the suggested reference range plasma levels of 5 to 45 µg/ml (11), although higher doses may be necessary in dogs also receiving phenobarbital. There is now an extended-release formulation that allows twice-daily dosing.

There is one study of levetiracetam’s efficacy in refractory epileptic dogs (12), in which 8 of 14 dogs had a reduction in seizure frequency greater than 50%. The only side effect reported was sedation in one of the dogs. A more recent placebo-controlled trial was completed in dogs with refractory epilepsy and failed to show benefit, which is probably a result of the pharmacoresistant nature of the cases combined with inadequate study power; however, this trial confirmed the drug's safety (13). An additional advantage of levetiracetam is that it is available intravenously and it is therefore starting to be used in patients with status epilepticus or cluster seizures. There is a recent report of the efficacy of intravenous levetiracetam used at a dosage of 30 to 60 mg/kg IV in dogs presenting with cluster seizures or status epilepticus. In all cases, seizures were first stopped by a benzodiazepine and then either the drug or placebo was administered (14).

Levels of levetiracetam in plasma can be measured at the pharmacology laboratory at Auburn at the same cost as zonisamide, but the lack of adverse side effects for zonisamide makes this less critical. It has also been noted in humans that the association between plasma levels and therapeutic effect is weak. Levetiracetam has been used in cats (15). It has a half-life of 3 hours, and three-times daily dosing of 20 mg/kg has been recommended. Seven of 10 cats with refractory epilepsy responded to treatment with levetiracetam, and only two showed side effects of lethargy and inappetence.

Management of Cluster Seizures in Refractory Epilepsy

Cluster seizures are defined as more than one seizure in 24 hours—they are a common problem for dogs with refractory idiopathic epilepsy. During an episode, some dogs seize every

4 to 12 hours, but others have more frequent seizures and, in some cases, full recovery of consciousness between seizures does not occur and they are more correctly considered to be in status epilepticus. In these cases use of a benzodiazepine becomes a critical part of the seizure control plan. One of the main objectives for owners of these dogs is to manage them at home, as the cost of regular visits to the emergency department is crippling. It is important to start by evaluating the patient afresh and optimizing blood levels of antiepileptic drugs that the patient is receiving. In the face of a bad cluster of seizures, increases in doses of existing drugs or the addition of a new antiepileptic drug may be necessary, with the primary aim of controlling seizures. Zonisamide and levetiracetam can both be added to each other and to phenobarbital and potassium bromide. Once seizures are controlled, doses are further adjusted to reduce side effects. It is useful to determine which drugs are most effective for the patient; owners' seizure logs can be examined for response to introduction or dose increases of a particular drug, and the drug with the most apparent efficacy can then be targeted for additional increases.

Equally important is development of rescue strategies for owners. Two approaches can be used. The first is to use benzodiazepines administered by the owners per rectum (PR) or by intranasal (IN) or intramuscular (IM) routes. First, owners must be given a detailed explanation of how to administer drugs by the proposed route, with practice demonstrations if needed. The main problems with the PR approach are difficulty inserting the catheter and failure of drug absorption if the rectum is full of feces. IN administration of drugs provides excellent absorption with rapid delivery to the brain (16). The drug can be dripped slowly into the nostrils, alternating from side to side; however, the main drawback of this method is difficulty administering into the nostrils (although purpose-made administrators are available)—it is difficult to deliver the drug into the nostrils of smaller animals, and it can be aspirated if administered too quickly. IM injection can be more challenging for many owners but for owners who are able to do this, it is an effective route of administration for midazolam (17). Diazepam can be administered at a dose rate of 1 mg/kg PR or IN (15) but *not* IM. It is important to remember that diazepam is light-sensitive and adheres to plastic; as a result, it needs to be drawn up from the glass vial at the time of administration. Midazolam is administered at a dosage of 0.25 to 0.5 mg/kg PR, IN, or IM (16). Lorazepam can be administered at 0.25 mg/kg IN but *not* PR (18). The use of diazepam in this manner has been shown to be effective in dogs (19). As benzodiazepines are short-acting, dogs that have seizures hours apart benefit from a longer-acting antiepileptic. Owners can administer a full dose of the antiepileptic that seems to be most effective in their dog once the seizure is over and the dog can swallow. This can be repeated after subsequent seizures as long as it is not done more frequently than once per hour. Owners should seek emergency care if they have given 3 extra doses of an antiepileptic drug over a period of 24 hours and their dog has another seizure.

Conclusion

The drugs discussed here have come to the fore because of their safety, ability to dose twice to three times a day, and now their affordability. New drugs come off patent all the time, and so the list of possible candidates for treating epilepsy will change. It is notable that there are no data available on the use of these agents as monotherapy for dogs or cats; however, this does not mean that they will not be effective, and we use them in this way more and more frequently. If they fail to control seizures, phenobarbital can be added.

References

1. Thomas WB. Idiopathic epilepsy in dogs and cats. Vet Clin North Am Small Anim Pract. 2010;40:161-179.
2. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. J Vet Intern Med. 1993;7:318-327.
3. Podell M. Seizures. In: BSAVA Manual of Canine and Feline Neurology. Platt SR, Olby NJ, eds. Gloucester: BSAVA; 2013: 117-135.
4. Talarico LR, Schatzberg SJ. Idiopathic granulomatous and necrotising inflammatory disorders of the canine central nervous system: a review and future perspectives. J Small Anim Pract. 2010;51:138-149.
5. Orito K, Saito M, Fukunaga K, et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. J Vet Pharmacol Ther. 2008;31:259-264.
6. Walker RM, DiFonzo CJ, Barsoum NJ, Smith GS, Macallum GE. Chronic toxicity of the anticonvulsant zonisamide in beagle dogs. Fundam Appl Toxicol. 1988;11:333-342.
7. Schwartz M, Munana KR, Olby NJ. Possible drug-induced hepatopathy in a dog receiving zonisamide monotherapy for treatment of cryptogenic epilepsy. J Vet Med Sci. 2011;73:1505-8.
8. von Klopmann T, Rambeck B, Tipold A. Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. J Small Anim Pract. 2007;48:134-138.
9. Dewey CW, Guiliano R, Boothe DM, et al. Zonisamide therapy for refractory idiopathic epilepsy in dogs. J Am Anim Hosp Assoc. 2004;40:285-291.
10. Smith Bailey K, Dewey CW. The seizuring cat. Diagnostic work-up and therapy. J Feline Med Surg. 2009;11:385-394.
11. Moore SA, Muñana KR, Papich MG, et al. Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. Am J Vet Res. 2010;71:337-341.
12. Volk HA, Matiasek LA, Luján Feliu-Pascual A, Platt SR, Chandler KE. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. Vet J. 2008;176:310-319.
13. Muñana KR, Thomas WB, Inzana KD, et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled, crossover trial. J Vet Intern Med. 2012;26:341-348.
14. Hardy BT, Patterson EE, Cloyd JM, Hardy RM, Leppik IE. Double-masked, placebo-controlled study of intravenous levetiracetam for the treatment of status epilepticus and acute repetitive seizures in dogs. J Vet Intern Med. 2012;26:334-340
15. Bailey KS, Dewey CW, Boothe DM, et al. Levetiracetam as an adjunct to phenobarbital treatment in cats with suspected idiopathic epilepsy. J Am Vet Med Assoc.

2008;232:867-872.
16. Musulin SE, Mariani CL, Papich MG. Diazepam pharmacokinetics after nasal drop and atomized nasal administration in dogs. J Vet Pharmacol Ther. 2011;34:17-24.
17. Schwartz M, Muñana KR, Nettifee-Osborne JA, et al. The pharmacokinetics of midazolam after intravenous, intramuscular, and rectal administration in healthy dogs. J Vet Pharmacol Ther. 2012 Dec 19. [Epub ahead of print]
18. Podell M, Wagner SO, Sams RA. Lorazepam concentrations in plasma following its intravenous and rectal administration in dogs. J Vet Pharmacol Ther. 1998;21:158-160.
19. Podell M. The use of diazepam per rectum at home for the acute management of cluster seizures in dogs. J Vet Intern Med. 1995;9:68-74.