What's new, what's tried-and-true: An update on small animal seizure management

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Veterinary neurologist Dr. Michelle Carnes discusses updated terminology and effective management of epileptic dogs and cats at Fetch San Diego, 2019.

Although some breeds, such as Australian shepherds, are more susceptible to seizures, epilepsy can affect any dog or cat. Is there anything new veterinarians need to know about small animal seizure management these days? Why yes, there is. Michelle Carnes, MS, DVM, DACVIM, a founding member of the Veterinary Neurosurgical Society, is delivering an update at the Fetch dvm360 conference in San Diego today during a session sponsored by PRN Pharmacal.

First off, Dr. Carnes says, let's talk terminology. In 2015, the International Epilepsy Task Force reclassified seizures based on cause in companion animals and also consolidated terminology.[1] The changes were intended to provide a common language for the classification of human and companion animal seizures, to "unmuddle" the common terminology used, and to streamline communications about epilepsy and seizures, both in research publications and clinical settings. Prior to this, a common language for terminology regarding seizures in veterinary medicine had not been officially defined.

While approaches to classification may have changed, treatment approaches largely remain the same. According to Dr. Carnes, the tried-and-true medications are still phenobarbital and potassium bromide, although some newer medications also should be considered.

Here, Dr. Carnes walks us through how to tell if a patient is truly having a seizure, classifying the seizure by etiology and phenotype, and deciding how to treat the patient or whether to refer.

Is it a seizure or not?
It seems obvious, but first and foremost, Dr. Carnes says, we need to be sure an animal is actually experiencing seizures. Not all "paroxysmal abnormal events" in pets fit the criteria. But smartphones give us a huge diagnostic advantage. Dr. Carnes encourages veterinary teams to advise pet owners, when they call for an appointment, to bring a video of the episode to the exam.

Tip: Encourage your pet owners to bring a video of seizure event to the exam.

Still, videos aren't foolproof, as some non-epileptic conditions can mimic seizures. Idiopathic head-bobbing (or head tremors) is a condition seen in young dogs, mostly pit bulls, Doberman pinschers, English bulldogs and similar breeds. These dogs have a "yes" or "no" orientation to their head-bobbing that usually ceases with a distraction, such as food or a walk. The animals are alert during these episodes, but the events can be scary for clients. Many dogs outgrow this condition, and typically it's a benign process.

Episodic neck pain with tremors, muscle spasms or shaking can also look like seizures. Commonly caused by cervical disk disease or Chiari-like malformation and syringomyelia, these events can be dramatic and intermittent, depending on the underlying cause.

It can also be challenging to distinguish "head-shaking seizures" from aggressive head shaking for other reasons. If the head shaking is a form of epilepsy, the dog will typically not be able to be roused or distracted from it. True head-shaking seizures can be very violent and are considered focal motor seizures.

What's the cause of the seizure?
There are now only three etiologic classes of seizure agreed upon by the International Epilepsy Task Force:

Reactive seizures are due to metabolic, systemic or other nonprimary brain disease.

Structural seizures are due to primary brain disease (e.g., degenerative disease, brain tumor, stroke).

Idiopathic epilepsy is subdivided into proven-genetic (breed-related), suspected-genetic, and epilepsy of unknown origin.

What type of seizure is my patient having?
Again, there are now only three phenotypic terms used to describe the type of epileptic seizure a pet is having.

Generalized seizures are what we called *grand mal* seizures in the past. These can be tonic, clonic or both (tonic-clonic). They are due to seizure activity involving both cerebral hemispheres, and they almost always produce a loss of consciousness.

Myoclonic seizures are still considered a generalized seizure disorder, but animals maintain consciousness. Episodes often start in response to a trigger, usually light or sound. Animals can experience facial tremors, head-twitching or the motion of "jerking back abruptly" in response to a trigger, and they can go in and out of the response. Wirehaired dachshunds are predisposed to a syndrome involving myoclonic seizures in response to sound. Myoclonic epilepsy can progress to a worse form of seizure activity, such as generalized seizures, or it can become more and more sensitive to a specific trigger. Myoclonic seizures can also be a manifestation of a more serious structural brain disease.

Focal seizures are what we previously called *partial seizures* or, incorrectly, *petit mal* seizures in animals. They involve only one cerebral hemisphere and patients typically maintain consciousness. Focal seizures can consist merely of periods of "absence"–a cat or dog just sitting there blinking or making chewing motions–or they may be too subtle to notice. They probably occur more often than we realize and can progress to, or precede, generalized seizures. Focal seizures may be an early stage of a progressive generalized epilepsy in some cases. "Our [epileptic] patients may experience focal seizures prior to developing generalized seizures; they just probably go unnoticed," notes Dr. Carnes.

When do I start long-term therapy?

There are no hard-and-fast guidelines here, but Dr. Carnes' approach is generally to initiate long-term therapy if an animal is experiencing more than one seizure in three months, any cluster activity (more than one seizure in a 24-hour period), any status events (seizures longer than five minutes) or any major problems associated with the seizures that are intolerable to clients, such as aggression, violent movement or behavior dangerous to clients or other pets, particularly in larger dogs.

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Realistically, though, veterinarians must also consider the client's ability or willingness to medicate, afford prescriptions, follow up with exams and bloodwork, and deal with any medication side effects. "You have to weigh the side effects of treatment versus seizure risk and frequency … all determined by which drug we choose and how bad the seizures are," Dr. Carnes says.

When do I refer to a specialist?

Dr. Carnes recommends referring to a neurologist if a patient is more than 5 or 6 years old at the age of onset of seizures or if the neurologic exam is abnormal in the interictal period, keeping in mind that the postictal period can last up to three or four days. A client should bring the patient in for a neurologic exam five or more days after a seizure. If the client notes any behavioral changes that aren't temporally related to the seizures, or if you're unsure that the event is clearly a seizure, a specialist referral is also a good idea.

Neurologists are also available to help with difficulty controlling seizures with medication, dealing with unusual or intolerable medication side effects, and knowing when to alter doses or switch medications. Clients don't necessarily have to pursue advanced diagnostic imaging to benefit from a neurology referral. However, if they choose to do the imaging, a diagnosis could lead to more definitive treatment options. For example, if a meningioma is identified, "we do remove meningiomas, and especially in cats it's often a cure," Dr. Carnes says. So it might be a good idea to consider an MRI.

Goals of seizure management

The primary goal of management is a good quality of life: to balance the effects of the seizures and the side effects of the medications with the pet's wellbeing. For most patients, this means less than one seizure every three months, no clusters, no status events, minimal side effects from medications, minimal changes in bloodwork (especially in liver enzyme activities), affordable therapy, and a protocol that's compatible with the owner's willingness or ability to comply.

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Treatment failures, general therapy guidelines and considerations for cats

If a drug fails, consider that you may have an incorrect diagnosis. Instead of epilepsy, the patient may have a primary brain disease that's progressing, or it's not experiencing seizures after all. Alternately, the owner may not be complying with the treatment plan, the animal might be developing a drug tolerance, or there may be a drug interaction with another nonseizure medication. Look up any drug interactions that could be decreasing the efficacy of your primary medication.

Dr. Carnes points out that she prefers to maximize the dose of the primary drug before changing to a different medication or adding a second. If you need a second drug, consider how sedated your patient is. For example, if you're using phenobarbital and the animal is not too sedated, Dr. Carnes would recommend potassium bromide. If the patient is significantly sedated, she would add levetiracetam instead.

Never use a "tiger top" tube for measuring serum blood concentrations of either phenobarbital or potassium bromide, as the gel can absorb drugs and will artifactually lower your results, Dr. Carnes says. Always use red-top tubes to collect samples for drug concentration submissions.

We have all heard about the dog that seizures only when it goes to the veterinarian. These patients can be treated. First try trazadone given prior to the visit. If this is ineffective, Dr. Carnes recommends pulse therapy with either extended-release (40 to 60 mg/kg by mouth twice daily) or immediate-release (40 to 60 mg/kg by mouth every eight hours) levetiracetam. Have the patient start the day before the appointment, treat the day of and the day after, and then stop. Levetiracetam is fast-acting with fast elimination.

For cats with epilepsy, phenobarbital is still the go-to drug. Never use potassium bromide in cats as it causes pneumonitis. Levetiracetam can be used, but it requires dosing three times daily, and this is sometimes difficult for owners. Compounded extended-release levetiracetam is not readily available, and the commercially available 500-mg extended-release tablets are large and cannot be cut. Liquid levetiracetam is available but, again, it has to be given three times daily. Zonisamide can be used in cats; it's longer-lasting in this species and can be given as a once-daily drug; however, some cats may require twice-daily dosing.

Anti-epileptic drugs

Drug choices are based on access, personal preference, cost and what the veterinarian thinks is best for a particular patient and client. Dr. Carnes reviews the specifics of each of the commonly used drugs today.

Phenobarbital is the old "tried-and-true" drug. It's often what Dr. Carnes starts with and her primary therapy in cats. As a monotherapy in dogs, it has 82% efficacy in reducing seizure frequency by half, which is the standard goal for drug studies.[2] Phenobarbital works at gamma-aminobutyric acid (GABA) receptors and takes 10 to 14 days to reach steady state using a maintenance dose. An oral or injectable loading dose of 15 to 20 mg/kg, divided into up to four doses over a 2- to 24-hour period (based on how soon you need it to work), is recommended for many dogs initially.

Always check phenobarbital blood concentrations and serum chemistry two weeks after starting the drug or any changes in dosing, and then three months later, as you may see blood levels drop due to increased liver metabolism. You expect linear pharmacokinetics with phenobarbital, so if you increase the dose by 25%, you expect a 25% increase in serum concentrations. Dr. Carnes' target phenobarbital range is 20 to 30 µg/ml, and she doesn't like to go above 30 µg/ml for too long. Drug concentrations should then be checked every 6 to 12 months afterward.

Dr. Carnes recommends a complete blood count (CBC) with serum liver values after two weeks of starting phenobarbital. In addition, she recommends checking liver enzyme activities every time drug concentrations are evaluated. If alkaline phosphatase (ALP) alone is rising (which indicates liver induction), she will not necessarily change her therapy, but if alanine transaminase (ALT) is rising (which indicates liver damage), she gets concerned, she says. She advises testing bile acid concentrations in the face of a rising ALT to see if phenobarbital is becoming a real problem for the liver. If this is the case, she says, use a different anti-epileptic drug.

The primary potential side effects of phenobarbital are sedation, ataxia, polyuria and polydipsia, polyphagia and drug interactions (it usually increases clearance of other drugs, reducing their efficacy, rather than leading to toxic accumulations). Leukopenia, thrombocytopenia and superficial necrolytic dermatitis drug reactions are very rare but can result in severe consequences if experienced.

Potassium bromide is also a GABA receptor drug. As a monotherapy in dogs it has 73% efficacy in decreasing seizure frequency by half and a 50% chance of producing a seizure-free state, which is more seizure-free dogs than with phenobarbital. It takes two to three months to reach a steady state, so Dr. Carnes often starts with a loading dose. She recommended 500 mg/kg added to the maintenance dose (40 mg/kg/day), all divided over one to five days.

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Ideally you would check serum drug concentrations immediately after loading (so on day six with the example of a five-day load), then at 30 and 120 days after starting the drug. If you see more than a 10% drop in your one-month concentration compared with the postload concentration (day six in this example), this indicates that the maintenance dose is not keeping up with the postload levels and you should increase the dose.

Potassium bromide follows linear pharmacokinetics like phenobarbital. Once you have reached a maintenance concentration, if the patient's seizures are well controlled, you can check concentrations yearly. Dividing the loading dose into several times a day helps prevent gastric irritation from the salt component, but while on maintenance dosing this is just a once-daily drug. A sudden change in salt intake (saltwater, diet changes) can drop concentrations abruptly and cause a seizure, but this is uncommon. Side effects may include sedation, ataxia, gastrointestinal upset and, rarely, pancreatitis.

Levetiracetam has a very short half-life of approximately four hours in dogs and cats. It is variably effective as a monotherapy. Some studies have shown no reduction in seizures, others up to a 52% reduction. [3, 4] Dr. Carnes does not often use it as a first choice for monotherapy; rather, she reported great responses using levetiracetam as an add-on therapy. The dose is 20 to 60 mg/kg three times daily, unless you have the extended-release tablets. These extended-release tablets cannot be broken for use in smaller dogs, though, and they come only in 500- and 750-mg sizes. There is no need to check blood concentrations and minimal liver metabolism; side effects are uncommon but may include mild lethargy. No loading dose is necessary for this drug. An injectable formulation is also available.

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Zonisamide is a sulfonamide drug that can be used as a monotherapy or an add-on therapy. Studies have shown a 60% efficacy as a monotherapy and a 70% reduction in seizures as an add-on therapy.[2] It appears to be more useful with focal seizures than with severe generalized seizures. You actually need to use a higher dose if the patient is already on phenobarbital. The dose is 5 to 10 mg/kg twice daily as a monotherapy or 10 mg/kg twice daily as an add-on to phenobarbital therapy. No therapeutic range has been established in

dogs or cats, but checking blood concentrations may be benefit some patients.

Do not use zonisamide if a patient is already sensitive to sulfa drugs. Side effects include sedation, decreased appetite and, rarely, bone marrow suppression. A CBC and serum chemistry profile are recommended prior to and a few weeks after starting therapy. Some animals will develop a tolerance to zonisamide, and it should never be stopped abruptly, as seizures will likely recur. Because of the available formulations, this drug is good for smaller dogs.

Imepitoin is a drug for noise aversion but is being used for seizure management in other countries. It is not currently available in the United States. It has a comparable efficacy to phenobarbital, and side effects are similar to phenobarbital but not as severe. Imepitoin can be used in cats.

Cannabidiol (CBD) is getting a lot of attention as a therapy for seizures in animals. One study using it as an add-on drug in seven epileptic dogs showed a 33% reduction in the number of seizures, but these patients were not classified as responders when compared with placebo.[5] Dogs in the CBD group also had a significant increase in serum alkaline phosphatase activity.[5] At this time there are currently no extensive studies in dogs; however, research is ongoing.

ACTUAL CASE EXAMPLE

An owner gave CBD (unbeknownst to Dr. Carnes) to his difficult-to-control epileptic dog for eight months. The dog was already on a moderate dose of phenobarbital. He had no seizures for those eight months, but his phenobarbital levels went from 30 to 50 µg/ml in that time. The dog became ataxic and weak, his liver values went "through the roof," and the dog died of liver failure shortly thereafter. Dr. Carnes warns veterinarians to "remind clients that CBD is still a drug!"

https://www.dvm360.com/view/cbd-forget-legal-issues-does-it-work-veterinary-patients

Since CBD is not regulated by the FDA (or any other regulatory agency), there is likely to be a wide variation in purity and other additives in the numerous formulations that are commercially available. In general, the oral bioavailability of CBD tablets is poor, while the transmucosal oil does reach high plasma concentrations when administered correctly, Dr. Carnes says. CBD is a potent inhibitor of cytochrome P450 and has a long half-life in dogs, so it could potentially cause problems with drug interactions or liver metabolism. Otherwise, CBD seems to have a pretty good safety profile.

The popular thinking regarding the use of CBD in epileptic pets originates from the treatment of human seizures with Epidiolex, now reclassified as a schedule 5 drug, in children with severe intractable forms of epilepsy called Dravet syndrome and Lennox-Gastaut syndrome.

"This drug is extremely expensive," Dr. Carnes says. It is not affordable, or easily available, for veterinary patients at this time, even if it was found to be effective. For a 50-lb dog, a twice-daily dose of 5 mg/kg would cost $450 per month. Dr. Carnes is not against CBD for use in the future for seizures, but at this time her conclusion is that CBD is "expensive, unregulated, and the purity is not [adequate]" for use in dogs for epilepsy.

Dr. Carnes also cautions that the regulatory environment surrounding CBD makes it risky for veterinarians to recommend the use of these products. According to a statement released by the AVMA in February 2019, we are at risk for both professional liability and civil litigation if there are adverse effects during the use of these products, or even if they do not work, while there are other proven therapies available.

Seizure management is a variable process that can be complex and sometimes frustrating. As the language becomes more universal, as more advanced imaging becomes available, and as more information is gathered, the guidelines may become more specific. Drug choices may expand as well. The *Journal of Veterinary Internal Medicine* is now free on the internet, and you can check out the *2015 ACVIM consensus statement* on seizure management for more specifics.[2]

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