

# Seizure: Diagnosis and Management

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Somewhere around 5% of all dogs and 1% of all cats will have a seizure at some point in their life, making this a fairly common presentation in emergency and general practice. This article will give background information about seizures as well as general diagnostic schemes and treatment protocols.

## Overview:

Technically speaking, a seizure is a group of neurons that are abnormally excited and are therefore firing in an uncontrolled and synchronous manner. While this pathophysiology is interesting, it does little to help the patients, clients and veterinarians that are dealing with seizures. Seizures are divided in to many different categories by many different authors, but in my mind are most usefully split in to generalized and partial seizures. Generalized seizures are defined clinically by a complete loss of consciousness which is usually followed by uncontrolled motor activity (i.e. a tonic clonic seizure). The electrical activity in this form of seizure involves the entire brain. Partial seizures occur when the electrical abnormality is restricted to a certain area of the brain and the clinical manifestations are therefore limited to certain body parts (i.e. the right side of body, the face, etc). There may or may not be a behavioral change associated with a partial seizure, which further divides this category of seizures in the simple and complex.

In domestic animals typically three phases are recognized: pre-ictal, ictal and post-ictal. The pre-ictal phase is a behavior change that heralds a seizure. This change is most often noticed minutes to hours prior to a seizure, but can occasionally be seen as much as a day prior to the seizure. The ictal period or ictus is the seizure itself and in the average patient will last less than 2 minutes without intervention. The post-ictal period is changes in the pet's behavior and neurologic exam. The average post-ictal period is on the order of 20 minutes to a few hours, but some dogs will have post-ictal periods that last for multiple days.

## Historical data and Examination:

When the diverse set of movements and behaviors that can comprise a seizure are taken into account, it is easy to understand how an owner could confuse another syndrome for a seizure. The most common owner proclaimed "seizures" that are not in fact seizures in my experience are vestibular episodes, tremors and severe neck pain. Historical questions should be directed very specifically at

describing the circumstances and behavior before, during and after an event. Questions of particular importance are directed at determining consciousness (i.e. "Did your pet respond to its name during the event?"), any lateralizing signs (i.e. circling to a particular direction) and duration of the event. The presence of autonomic signs (i.e. urination) or a post-ictal period can also be supportive than an event was a seizure. Historical data that is helpful in the differential include signalment and any other behavioral or functional abnormalities in the past several months. In older patients a behavior change is often written off by owners as "getting old" and should be specifically investigated in the history. Similarly, a new proprioceptive deficit is some times wrongfully attributed to arthritis.

Neurologic examination of a seizure patient is ideally done a day or more after a seizure as to decrease the possibility of confounding neurologic deficits from the post-ictal period. Practicalities, not the least of which is a client who is quite upset about the seizure, mean that most patients end up in the emergency room or at our practice door within hours of their first witnessed seizure. In this circumstance, the presence of behavior changes and symmetrical findings such as bilateral menace or proprioceptive deficits should be interpreted with caution. Often these findings resolve on their own and do not indicate a structural lesion within the brain. Seizures arise from the prosencephalon- the cerebral hemispheres and thalamus. Asymmetric deficits are a strong indication of a lesion within the brain. Exam findings of note include asymmetric menace response deficits, proprioceptive deficits (especially with a normal gait), nasal sensation deficits and circling/pacing. A VSA neurologist will always be happy to examine and/or consult by phone on any patients that you have concerns or questions about.

### **Differential Diagnosis**

The full differential list for seizures is long, but can be generally grouped in to three categories: metabolic disease, structural disease of the brain and idiopathic epilepsy. I find this especially useful in my conversations with clients as it also provides a useful framework to discuss diagnostics: bloodwork investigates metabolic causes, MRI and spinal tap investigate structural disease and idiopathic epileptics will be normal on all tests.

The most common metabolic conditions to cause seizures include hepatic encephalopathy, hypoglycemia and toxins. Diagnostic testing to rule out metabolic disease includes CBC, chemistry and liver function testing (i.e. pre and post prandial bile acids). Toxins are best ruled out in the history, but specific toxin assays do exist. Methylxanthines, bromethalin based rodenticides, lead and prescription medications are common seizure inducing intoxicants. Tremorgenic

toxins such as metaldehyde, pyrethrins and tremorgenic mycotoxins can also induce seizures, but this is less common than a tremor presentation.

The type of structural brain disease likely in a particular patient depends heavily on signalment. Any patient over the age of 5 years old at first seizure is suspicious for a tumor, particular if they are a Boxer or Golden Retriever. Inflammatory diseases like GME or necrotizing encephalitis are more common in young to middle age small breed dogs and there may be a predisposition towards females. Infectious in general are rare, but seem to be more common in young adult animals. Anomalies are common in pets less than 1 year of age, hydrocephalus being the most common. In general, structural disease of the brain is investigated with a combination of MRI, spinal fluid analysis and infectious disease testing.

Idiopathic epilepsy is in the most strict sense a diagnosis of exclusion. As with any idiopathic condition, to truly know that something has no discernable cause we must look for all other causes. However most dogs that begin to have seizures between 2 and 5 years of age, have normal inter-ictal neurologic exams and normal bloodwork are safely diagnosed with presumptive idiopathic epilepsy. I will often mention the MRI to these clients, but discuss that it is not a necessary diagnostic unless seizures are particularly difficult to control or additional neurologic signs develop. The possible exception to this is the Pug or to a lesser extent other small breed dogs, because of the high incidence of necrotizing encephalitis (formerly called Pug/Yorkie encephalitis) within these breeds. Necrotizing encephalitis can present initially with only seizures until a rather sharp neurologic decline. Therefore, I recommend referral to a neurologist for examination and an MRI in any small breed dog with seizures despite their age and neurologic examination.

While idiopathic epilepsy does occur in cats, cats are preferably fully worked up as other diseases such as infections (FIP, toxoplasma) and neoplasia are as likely, if not more common, causes of seizures.

### **Emergency Treatment:**

When presented with a patient who is actively having a seizure, I will reach for a benzodiazepine first unless the patient is in liver failure. Patients with liver failure will be addressed later in this discussion. Valium can be given intravenously or intranasally at a dose of 0.5mg/kg, and rectally at a dose of 1mg/kg. The nasal and rectal routes of administration are particularly helpful in a patient without an intravenous catheter already in place.

Should the benzodiazepine not work the first time, I will give it two more times over the course of 5 minutes. Should the drug pause the seizure but not stop it entirely, or if the patient has another seizure within several hours, a benzodiazepine CRI is recommended. Whatever dose stops the seizure, however briefly, is given as a CRI. For instance if 0.5mg/kg of valium results in a pause in status epilepticus, then a 0.5mg/kg/hr valium CRI is recommended. This CRI is increased by 0.05-0.1mg/kg/hr if another seizure occurs, and decreased by 0.1mg/kg/hour every 2 hours should no seizure occur after 6 hours on the CRI. Any animal requiring a CRI or other additional measures to stop a seizure would best be managed at a 24 hour facility for titration of the medications and monitoring.

If the benzodiazepine is ineffective or only partially effective, a loading dose of a maintenance anticonvulsant is recommended, particularly if the patient is not currently on an anticonvulsant. Phenobarbital can be given intravenously, which makes it ideal in this context. The full loading dose (15-20mg/kg) can be split in to two or three doses or can be given as a single dose. Potassium bromide can also be loaded rectally in an emergency. The loading dose is 400-600mg/kg. This dose is generally given over a period of several days to prevent severe sedation and ataxia, which somewhat limits its use in emergencies.

A majority of emergency anticonvulsant drugs cause respiratory depression, which becomes more likely as higher doses and multiple drug classes are used. If the patient in status epilepticus requires multiple doses of any intubation and ventilation may be necessary. Additionally, attention should be paid to body temperature, and an in-house blood glucose level should be taken both for diagnostic and treatment purposes.

Should both benzodiazepines and loading maintenance medications be ineffective, intravenous levetiracetum (Keppra) is recommended at 60mg/kg IV. If ineffective levetiracetum may be followed by another barbiturate- usually thiopental now that pentobarbital is more difficult to obtain. Doses are identical to those used to induce general anesthesia, and intubation and ventilation is very likely to be necessary at this point.

It should be noted that some would reach for propofol prior to thiopental, including my colleague Dr. Vitale. Certainly this treatment is still well within the standard of care, and is considered the rational next step by a good number of very intelligent clinicians in both the veterinary and human medical fields. However, propofol can cause seizure like phenomenon in both epileptic and non epileptic patient when used as an induction agent, which gives me pause in using it in this context. Additionally, I find the tremors and twitches that are common in

patients recovering from propofol make it difficult to monitor a patient recovering from status epilepticus. Therefore I rarely reach for propofol, and reserve its use in cases where all other options have been ineffective.

Status epilepticus that does not respond to induction of general anesthesia carries a grave prognosis. Other agents that maybe tried include gas inhalants such as isoflurane. There is one report of using ketamine in a dog with unresponsive status epilepticus. In general, these patients should be referred to a neurologist on an emergency basis for additional diagnostics so that underlying causes may be identified and addressed in a timely manner.

Liver failure patients present a different set of challenges when in status epilepticus. Patients in liver failure are theorized to have increased endogenous benzodiazepine like compounds due to their disease, and additionally will metabolize benzodiazepines less efficiently. This makes the typical first line drug of choice (valium) less desirable due to excessive sedation and respiratory depression. The underlying problem should be addressed via a lactulose retention enema. As for acute anticonvulsant medication- intravenous levetiracetam works well and is not metabolized by the liver. If levetiracetam is not on hand, low doses of benzodiazepines may be tried with caution. The dogs can also be loaded rectally on potassium bromide. However, this loading can result in diarrhea, especially when given in concert with a lactulose enema.

### **Maintenance Treatment, first-line anticonvulsants:**

Maintenance treatment of seizures presents a different set of challenges. Most veterinarians have seen a good number of seizure patients and therefore have some familiarity with phenobarbital and potassium bromide.

The first decision to be made with maintenance medication is when to start medication. There seems to be a general consensus that more than one seizure in a four to six week period warrants treatment in most animals. However, the decision to start treatment is an intensely individualized decision based on the patient, the type and severity of seizures and the owners' tolerance of the seizures. It is important to stress that once medication is started it is frequently a lifelong treatment.

Side effect profiles for phenobarbital and potassium bromide are similar with some notable exceptions. Both drugs commonly cause polyphagia, polydipsia, polyuria, sedation and ataxia. The ataxia and sedation are often transient; waning to minimal effect in 10-14 days. These side effects are most prominent after starting a new drug or increasing the dose of a current drug. Other noted side

effects with phenobarbital are liver enzyme induction, and rarely liver failure. Additional side effects of phenobarbital, like blood dyscrasias and cutaneous drug reactions are rare.

Potassium bromide will cause vomiting, especially with tablet forms or in patients who receive the drug without food. The liquid bromide formulation is the preferred by most neurologist as it seems to be better tolerated and absorbed, and dose adjustments are easier to make. It should be noted there is a new FDA approved form of bromide for dogs which legally restricts compounding of bromide for our patients. Compounding was previously the only way to obtain bromide, so this represents a significant shift in the use of this drug. Dietary salt intake will alter the excretion of bromide, so dramatic shifts in salt intake (i.e. eating salty foods or drinking ocean water) can vastly alter the blood concentration of bromide. Similarly, IV fluid therapy will rapidly wash out the bromide in a patient. This is used to treat bromide toxicity, but in my experience is most commonly encountered as a problem in the stable epileptic who is hospitalized on IV fluids for another problem. Potassium bromide has been associated with pancreatitis in dogs, but this link is tenuous at best. Cats generally should not be treated with bromide, as it may be less effective as an anticonvulsant in and will induce an asthma-like lung condition in a large percentage of patients.

As most of us have learned by experience, the first dose of anticonvulsant prescribed for a patient is uncommonly the dose they are on for the rest of their lives. Taking side effect profiles into account, either drug makes an excellent first line anticonvulsant choice. Phenobarbital is dosed at 2-5mg/kg every 12 hours. Patients that who are suspected to have an underlying structural lesions or those that have a more severe seizure type at the onset of disease (cluster, status, more than 4 seizures per month) should be started at a higher dose (3-4mg/kg) as these patients are generally more difficult to control. Bromide is dosed at 20-30mg/kg once daily as an add-on anticonvulsant and 30-50mg/kg once daily as a first line anticonvulsant. Higher doses are reported, up to 90mg/kg, however I have never seen a patient that could reasonably tolerate that dose without severe side effects.

Patients who are not controlled on a certain dose of either drug should be increased by 25% until blood levels reach the top end of the therapeutic range or side effects are intolerable. It is vastly preferable in my mind to "max out" one drug before adding a second anticonvulsant. An orderly approach to seizure management is key in managing this sometime frustrating symptom.

Time to steady state becomes important when prescribing these medications and also when testing blood levels. Phenobarbital takes 10-14 days to reach steady state and potassium bromide takes 3-4 months. Both drugs can be given at higher doses to achieve therapeutic concentrations more rapidly, which is called loading; however the animal's maintenance blood levels will still stabilize at the above mentioned time period. It is recommended that baseline levels are submitted after a dose change reaches steady state and routinely at least once a year. For phenobarbital I prefer levels twice a year for maintenance monitoring. Blood levels that are taken before an animal has reached steady state have some role in emergency management, but minimal value for maintenance therapy. Concurrent with the levels, a pre and post prandial bile acids panel should be checked in patients on phenobarbital and renal disease panel checked in patients on bromide. Bromide does not cause renal disease, but as it is entirely excreted by the kidney, renal dysfunction can alter bromide levels. A standard liver panel can also be run in patients on phenobarbital; however expected hepatic enzyme induction can preclude accurate interpretation of this test.

Levels are used to monitor therapy. No one level guarantees a patient will be controlled, but trends and changes can be crucial to appropriate management. This is especially important as phenobarbital can induce its own metabolism via the p450 system, and does so randomly.

An additional benefit, especially with phenobarbital, is monitoring for potentially side effects. Dogs who are held at high blood level of phenobarbital chronically are more likely to develop liver failure. Additionally, patients on either phenobarbital or bromide who are uncontrolled and at the top end of the therapeutic range are in my experience unlikely to reach control on that drug and further drug increases are usually unrewarding.

The appropriate use of these two anticonvulsants is reported to control 75% of idiopathic epileptics. The other 25% patients are much more challenging, and will often require the use of so-called "second-line" or "add-on" anticonvulsants. It may be impossible to adequately control some of these dogs, and many will be euthanized due to uncontrolled seizures and/or the financial and emotional strain of this disease on their owners.

### **Maintenance Treatment, second-line anticonvulsants:**

The three newer drugs that I use most frequently are gabapentin, zonisamide and levetiracetam. As these drugs are relatively new, we are still learning about them and the information can seem to change on a month to month basis. They have been evaluated for safety in dogs, and in general have fewer side effects

than either of the standard anticonvulsants. Literature regarding use in cats is sparse, but some new trials are underway. Multiple drug mechanisms have been suggested for each of these medications, but the true mechanism of action is unknown. Blood levels are available for all of these medications through Auburn University. As therapeutic ranges have yet to be firmly established, results should be interpreted with caution. Levels can be somewhat helpful in a comparative context (i.e. the medication was effective at level X and now is not effective at level Y), but otherwise they are mainly of academic interest. Previously many of these drugs were cost prohibitive, however the arrival of generic forms on the market has significantly reduced the cost. Along those lines, due to previous cost and unfamiliarity they have been primarily used as add-on or rescue therapy in patients unresponsive to bromide and phenobarbital. With the arrival of cheaper generics and increasing knowledge, they are being considered more frequently as first line drugs in a variety of patients.

Gabapentin and zonisamide have anecdotally been used in cats with some success and minimal side effects. However, there is a published favorable clinical trial of the use of levetiracetam in cats, making this the current add-on drug of choice in this species.

Levetiracetam is also the second-line drug of choice in patients with liver disease. It is also, as mentioned, helpful as an IV bolus in patients in status epilepticus. The majority of the drug is excreted unchanged in the urine. In general this drug is extremely well tolerated. I have only encountered sedation as a significant side effect a patient in oliguric renal failure. The drug is dosed starting between 20-40mg/kg every 8 hours and is increased by 20mg/kg increments until it becomes cost prohibitive. It has been reported that some patients will return to their original seizure frequency within 8 months of starting levetiracetam, which has been termed "the honeymoon effect". The honeymoon effect has been anecdotally reported with other add-on anticonvulsants, but this has not been confirmed in the literature.

Zonisamide has many attractive qualities over levetiracetam and gabapentin, particularly since it is dosed twice a day rather than the three to four times. I also feel that my long term success rate is a bit higher with this medication compared with the levetiracetam or gabapentin. It is partially metabolized by the liver, so must be used with caution in patients with liver disease. However it has not been reported to cause toxicity, so it can be considered in these patients. The starting dose is 5mg/kg every 12 hours. Due to hepatic microsomal enzyme induction, patients that are currently on phenobarbital should be started at 10mg/kg every 12 hours. Side effects are minimal, and are usually restricted to mild GI upset. The lack of significant sedation or ataxia caused by this medication is particularly

helpful in patients with pre-existing deficits that we do not wish to make more sedate or ataxic, even temporarily.

Gabapentin is only moderately effective as an anticonvulsant. It is more useful in the treatment of neuropathic pain, such as exist in caudal occipital malformation syndrome. In human beings, it is more effective in treatment of partial seizures, but this association has not been confirmed in veterinary patients. The starting dose is 10mg/kg every 8 hours, and some dogs may require up to 20mg/kg or dosing every 6 hours. The human liquid gabapentin formulation is manufactured with xylitol at near toxic levels in the therapeutic dose range. Therefore, it is strongly recommended that all patients who require the liquid formulation have it specifically compounded without xylitol.

In general if you have a complicated case or would like to discuss using a newer anticonvulsant medication I recommend you contact a VSA neurologist for a phone consultation.