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SEIZURE MANAGEMENT:
DIAGNOSTIC AND THERAPEUTIC PRINCIPLES

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INTRODUCTION
Seizures are paroxysmal, synchronous neuronal discharges typically originating in the cerebral cortex. Epilepsy is a general term that refers to recurrent seizures of any type and can be divided into different etiologic categories1,2:

1. **Primary or idiopathic epilepsy.** Seizures that occur in the absence of obvious structural brain disease. An inherited basis is usually implied and has been proven in many popular breeds of dog such as the Labrador retriever, the German shepherd dog, the golden retriever and the dachshund. Many other breeds are also affected.

2. **Secondary or symptomatic epilepsy.** Seizures result from a specific brain disorder such as a brain tumor or encephalitis.

3. **Cryptogenic or probably symptomatic epilepsy.** No known cause for the seizures is identified, but the seizures are suspected to be secondary (symptomatic).

4. **Reactive epilepsy.** Seizures result from an extracranial disease such as hypoglycemia.

Seizures can be divided into generalized and focal seizures. Generalized seizures involve the body symmetrically and are typically (but not always) tonic-clonic (grand mal). The seizure starts with the tonic phase (limb extension) and loss of consciousness, and this is followed by clonus (limb flexion) and is often accompanied by autonomic signs. Petit mal, or absence seizures are also generalized, but are rare in domestic pets. Petit mal seizures are characterized by a brief change in consciousness and are frequently unrecognized. Focal seizures are caused by a focal disruption of neuronal activity and historically have been associated with secondary epilepsy. However, more careful evaluation of the signs shown by dogs with presumed idiopathic epilepsy has revealed that many of these dogs have focal seizures.3 It is therefore becoming accepted that the presence of a focal seizure does not rule out primary epilepsy. The signs reflect the area of cortex that is affected, for example a lesion in the left motor cortex will produce twitching of the right side of the body, and a lesion in the visual cortex may produce fly biting. A lesion within the limbic system can produce disturbing alterations in behavior (screaming, viciousness, somnolence) previously known as psychomotor seizures, but now called complex focal seizures. Focal seizures can generalize (spread to involve the whole cortex, producing more typical generalized seizures).2,3

CAUSES OF SEIZURES
Causes of seizures can be divided into intra- and extracranial categories (see table on following page for full list). Extra-cranial causes include metabolic problems (e.g. hypoglycemia, portosystemic shunt, electrolyte disturbances, hyperlipemia) and toxicity (e.g. lead, ethylene glycol). Intra-cranial causes include neoplasia, infectious/inflammatory disease, hydrocephalus, trauma, vascular disease, and primary epilepsy. Many different genetic causes of epilepsy have been characterized in humans and rodent models. Aberrations in genes encoding ion channels, and in mitochondrial genes are examples of genetic causes of epilepsy. Several different groups are now examining the canine genome in families of epileptic dogs to identify causative mutations. It is very likely that tests for carrier and affected status will be developed form familial (primary) epilepsy in the next decade.

IDENTIFICATION OF SEIZURES
Generalized seizures are usually easy for owners to recognize, but many ‘episodes’ can be more difficult to define, especially as they are rarely witnessed in the clinic. Useful points to ascertain include whether the animal goes stiff (versus limp in syncopal episodes), falls over, loses consciousness, or develops autonomic signs (urination, defecation, salivation), and whether there are any pre- or post-ictal signs. Cats in particular can have unusual seizures in which autonomic signs (typically the cat develops hiccups and salivation), or bizarre behavior (yowling, frantic running) predominate. Seizures are more likely to occur when the animal is resting in contrast to syncopal events so it is worth establishing when episodes occur from the owner. It is often useful to ask owners to video-tape episodes, and to get them to check a heart rate and mucous membrane color during an episode if you feel it might be syncopal. Dr O’Brien of the University of Missouri has authored an excellent web site complete with video clips of different seizures that may be useful for owners to review (http://www.canine-epilepsy.net/basics/basics_index.html).

DIAGNOSIS OF SEIZURE DISORDERS
The most effective seizure management is possible when a diagnosis has been made. Causes of seizures are listed in the table below:

The presenting signalment, history and clinical signs allow prioritization of differential diagnoses and selection of appropriate diagnostic tests.4 When symptomatic or reactive epilepsy is suspected (e.g. a 12 year old golden retriever with new onset of seizures), a full diagnostic evaluation including a minimum data base, a bile acid tolerance test, imaging of the brain, and analysis of cerebrospinal fluid should be recommended. In many cases, a full evaluation is not vital at first onset of seizures (e.g. an otherwise healthy 3-year-old German shepherd dog with recent onset of seizures), but a minimum data base, bile acid tolerance test and fundic exam is always recommended. The bile acid tolerance test not only rules out a portosystemic shunt, but also gives a baseline measure of liver function that can be referred to at a later date if the animal is placed on a hepatotoxic drug such as phenobarbital. All owners can be given a list of signs to watch for that might indicate an underlying brain disease (behavioral changes, stumbling, visual deficits) and therefore a need for a more complete diagnostic work-up.
Table 1 – Causes of Seizures

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>EXTRACRANIAL</th>
<th>INTRACRANIAL</th>
</tr>
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<tbody>
<tr>
<td>Degenerative</td>
<td>Lysoomal storage disease</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Anomalous</td>
<td>Lysosomal storage disease</td>
<td>Lissencephaly</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hydrocephalus</td>
<td>Porencephaly</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Thiamine deficiency</td>
<td>Primary brain tumor</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Primary brain tumor</td>
<td>Metastatic tumor</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>GME/Necrotizing encephalitis</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Viral (CDV, FIV, FeLV, FIP)</td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myotic (Cryptococcosis, Blastomycosis, Histoplasmosis, Coccidiodomycosis)</td>
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<tr>
<td></td>
<td></td>
<td>Protozoal (Toxoplasmosis, Neosporosis)</td>
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<tr>
<td></td>
<td></td>
<td>Rickettsial (RMSF, Ehrlichia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parasitic (Heartworm, Cuterebra)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Primary epilepsy, cryptogenic epilepsy</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Cranial trauma</td>
<td></td>
</tr>
<tr>
<td>Toxins</td>
<td>Lead, heavy metals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organophosphates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strychnine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metaldehyde</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethylene glycol</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Feline ischemic encephalopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhage (hypertension)</td>
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</tbody>
</table>

The most common presenting sign for a brain tumor is seizures, and this is frequently the only sign of the disease.\(^4\) It is therefore extremely important to recommend brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI) in any dog with new onset of seizures that is over 6 years of age. Certain breeds are predisposed to specific diseases and so the signalment will also guide the recommendations made. For example, new onset of seizures in a 4-year-old Boxer is more likely to be due to a brain tumor than primary epilepsy. Similarly, new onset of seizures in a 2-year-old pug is most likely a result of encephalitis. Cats are more prone to hypertension and its consequences than dogs, but in both species it is important to try to obtain a blood pressure measurement and to examine the retina for any evidence of vascular or other disease.

WHEN TO TREAT SEIZURES

Most seizure disorders cause recurrent seizures that are progressive in nature because of gradual recruitment of additional neurons to seizure foci (kindling). If an underlying cause for the seizures can be identified, treatment should be directed at that cause. Use of anti-epileptic drugs is indicated when a diagnosis of primary epilepsy is made, or when treatment of the underlying cause of the seizures in secondary epilepsy does not control seizures (e.g. animals with brain tumors, hydrocephalus or encephalitis). It is important to establish seizure frequency prior to initiating treatment as anti-epileptic drugs have side effects and may not be necessary. For example, if seizure treatment is initiated after the first seizure, it will never be clear whether this was going to be the only seizure the animal ever had, and it will be difficult to know whether to stop the medications or not. An exception to this guideline is when a diagnosis has been made and any further seizures could be life threatening. For example, if the animal has one seizure and a brain tumor is diagnosed, further seizures could cause fatal increases in intracranial pressure and the animal should be started on anti-epileptic drugs immediately. A more general rule of thumb is that seizures should be treated when they occur more frequently than once a month, when they occur in clusters or are associated with status epilepticus, or when they are associated with unacceptable side effects (e.g. an extremely prolonged post ictal period, viciousness, or airway obstruction in brachycephalic breeds of dog).\(^5\) In all instances, the most effective treatment requires full owner understanding and compliance. It is important to determine each owner’s expectations prior to initiating therapy.

WHAT DRUG TO USE: DOGS

In dogs the two main drugs used to treat seizures are phenobarbital and potassium bromide.\(^5,6\) Both drugs are effective when used alone and when used in combination. Primidone is not recommended because of hepatotoxicity, and oral diazepam is not an effective maintenance oral anti-epileptic drug in dogs due to its short half-life in this species. Phenobarbital has a half-life of 48 to 72 hours and should be
dosed orally twice a day. Starting dose is 2 – 4 mg/kg p.o. twice a day, and steady state is reached in 10 - 14 days. If rapid control of seizures is needed (for example, a dog presents with cluster seizures), administering 12 mg/kg split over 24 - 48 hours will achieve therapeutic blood levels of phenobarbital, although this will cause transient sedation. The advantages of phenobarbital include good efficacy, availability, reasonable cost, convenient dosing regime, and rapidity with which changes in dose are reflected in blood levels, making dose adjustment straightforward. Disadvantages include record keeping (it is a controlled drug), polyphagia, PUPD, initial sedation (should resolve in about one week), and sedation when higher blood levels are necessary, hepatotoxicity (most frequently associated with blood levels of greater than 35 microg/ml), neutropenia and thrombocytopenia (a very rare complication), necrotic dermatitis, and drug interactions (should not be used in conjunction with cimetidine, chloramphenicol or ketoconazole). Tolerance to phenobarbital may develop, necessitating higher doses to maintain the same blood level over time. Therapeutic blood levels range from 15 – 45 microg/ml, although levels of greater than 35 microg/ml are associated with an increased risk of hepatotoxicity. Once steady state is reached, changes in dose to achieve a desired blood level can be calculated using the following equation:

New dose = current dose X desired blood level / measured blood level.

The dose required is dictated by the frequency of seizures, the blood level of the drug and the severity of side effects seen. Dogs treated with phenobarbital should be monitored every 6 – 12 months with a physical examination, measurement of phenobarbital blood levels and a chemistry panel to check for signs of hepatotoxicity. A sudden large increase in liver enzyme values (expect them to be moderately elevated when on phenobarbital), or a decrease in albumin should be investigated further with a bile acid tolerance test. It should be noted that abrupt discontinuation of treatment of seizures (with either phenobarbital or potassium bromide) can result in fatal status epilepticus or the recurrence of seizures that are more difficult to control.

Potassium bromide has been used with great success as an addition to phenobarbital therapy in dogs with refractory seizures. It is now increasingly being used as a single agent in dogs. Potassium bromide has a long half-life ranging from 24 – 46 days in dogs depending on the dietary salt content and renal function. It should be dosed once a day at a rate of 25 - 40 mg/kg/day and steady state is reached in 3 – 4 months. In order to achieve therapeutic blood levels (100 – 300 mg/dl) more quickly, it can be loaded by dosing at a rate of 100-130 mg/kg/day for 5 days, then decreasing the dose to the maintenance of 30 mg/kg. The blood level should be checked after the 5-day loading dose and again 4 – 6 weeks later to ensure that therapeutic levels are maintained. In case of emergency, therapeutic levels can be achieved in one day by oral administration of 200 mg/kg with a little food 3 times at 2 – 3 hour intervals (total dose of 600 mg/kg). The advantages of potassium bromide include good efficacy particularly when used in addition to phenobarbital therapy, lack of hepatotoxicity, once daily dosing, reasonable cost and lack of controlled drug status. Disadvantages include PUPD and polyphagia, sedation and hind limb weakness when at high blood levels (particularly in combination with phenobarbital), lack of approval for veterinary use, need for a consistent diet (changes in salt content of the diet change drug blood levels), gastrointestinal irritation, a skin condition called bromoderma and possibly an association with hyperlipemia and pancreatitis. Potassium bromide is available in liquid and capsular forms. Capsules are said to be associated with a higher frequency of gastrointestinal side effects as the dissolving capsule provides a focus of the salt solution within the stomach. Gastrointestinal irritation can be minimized by administering the drug with food.

When deciding whether to start treatment with phenobarbital or potassium bromide or a combination of both drugs, a number of factors can be considered. For example, if the dog is very young, it might be desirable to start treatment with potassium bromide and only add in phenobarbital if necessary to minimize the time the dog may be receiving a hepatotoxic drug. In animals presenting with a severe cluster of seizures, it is usually preferable to start immediate treatment with phenobarbital, because steady state blood levels can be reached more quickly and the drug can be administered intravenously. If it is not possible for the owner to administer a drug every 12 hours, potassium bromide may be the drug of choice because it can be administered every 24 hours. Finally, drug side effects should be taken into account and dogs with liver disease should not be treated with phenobarbital, while it may be advisable to avoid potassium bromide in dogs with a history of pancreatitis.

MANAGING THE CHRONIC EPILEPTIC DOG

Following initiation of treatment, the owners should be asked to keep a log of seizures including a description of the event and post ictal signs. Blood levels of the drug used should be measured about 5 half lives after starting treatment (10-14 days for phenobarbital, 3 - 4 months for potassium bromide unless a loading dose was used), and at that time the severity of side effects can be assessed. Measurements of trough levels of drugs were recommended historically, but recent work suggests this is only necessary in problem cases. If seizure frequency is greater than one a month (or severe clusters etc as discussed above), then the first thing to do is measure blood levels of the drug and evaluate the dog to ensure that no additional neurological signs have developed, indicating a different underlying problem. To address the increased seizure frequency, the dose of the anti-epileptic drug being administered can be increased in direct proportion to the desired increase in blood level. Alternatively, a second drug can be added into the treatment protocol (either phenobarbital or potassium bromide). Typically, I will make sure the blood level of phenobarbital is between 25 and 30 microg/ml and potassium bromide is greater than 150mg/dl prior to adding in a second drug. However, in some cases there may be a good reason to add in a second drug without having attained these blood levels. For example, if the animal is showing signs of liver disease, potassium bromide should be added in as soon as possible to minimize the dose of phenobarbital necessary.

When seizure frequency is not adequately controlled by the above drugs, or unacceptable side effects occur, effective seizure treatment becomes problematic and expensive. Felbamate (Felbatol), gabapentin (Neurontin), levetiracetam (Keppra) or zonisamide (Zonegran) can be added to potassium bromide and phenobarbital. Their efficacy has not been tested objectively as yet, and the relatively limited number of dogs treated so far means that we are still learning about all the side effects and beneficial effects of these drugs. These drugs are discussed in further detail in the session on refractory seizures.
WHAT DRUG TO USE: CATS

Phenobarbital and potassium bromide can be used as antiepileptic drugs in cats. In addition, benzodiazepines can be used orally in this species. The drug doses, efficacy and side effects are discussed in more detail in another manuscript.

MANAGING STATUS EPILEPTICUS

Status epilepticus is an emergency that every practicing veterinarian will have to deal with at some time or other. Management of such cases is enhanced by having an emergency protocol ready at hand and by having intravenous phenobarbital available. There are many different drug doses cited and each case needs to be managed differently, but an example of a protocol is given below:

1. Establish venous access.
2. Give 0.5mg/kg diazepam iv. If can’t give iv, give same dose per rectum.
3. Pull blood and check glucose immediately. Submit stat CBC, chem panel, UA +/- bile acids/ammonia. Check phenobarbital and/or bromide levels if appropriate.
4. Check body temperature and treat appropriately.
5. If glucose is low (60mg/dl or less) administer glucose. As a rough guideline: 200mg/kg glucose iv should increase blood glucose by 100mg/dl. 50% dextrose is 500mg/ml, ie 0.4ml/kg: dilute to 10% before giving.
6. Be suspicious of hypocalcemia in certain instances: a bitch that has whelped; a dog that has had parathyroids removed surgically. Dose: 4ml/kg of 10% calcium gluconate iv slowly.
7. If diazepam doesn’t work, repeat twice. You can start an iv infusion, (but be sure to try appropriate phenobarbital therapy first or in conjunction), use the dose that stops the seizures when given as a bolus, and give this dose per hour as an infusion. Remember to coat the plastic and to protect from light. Remember that IV diazepam does not give long term seizure control.
8. If still seizing or seizures recur rapidly, move onto phenobarbital: loading dose is 12 – 16mg/kg iv. You will not usually give this as one bolus. Start with 4 - 6 mg/kg boluses if the dog is not already on phenobarbital. If animal is already on phenobarbital, give 2 – 4 mg/kg phenobarbital iv boluses. This will increase blood levels by about 2 – 4 ug/ml. Note that iv phenobarbital takes 15 – 30 minutes to take effect. In cats, give 2- 4mg/kg iv boluses. Note: some clinicians do go ahead and give 12mg/kg phenobarbital as one bolus in dogs that are not already on phenobarbital: if you plan to do this be ready to ventilate the animal.
9. If seizures stop continue maintenance dosing of phenobarbital: 2mg/kg po or iv BID (if not already on phenobarbital), or increase current dose if already on phenobarbital. If comatose start on maintenance fluids.
10. If seizures don’t stop
   a) Make sure you haven’t missed a metabolic problem (glucose, calcium, liver failure).
   b) Check for evidence of other underlying disease
   c) Move on to anesthesia: there are several options:
      (i) phenobarbital: 1 – 3mg/kg iv: give slowly and watch for seizures to stop. Follow up with a blood gas to check the animal is not hypoventilating. Intubate and ventilate if necessary. You often end up needing a lot more than 3mg/kg, but this is a nice guideline for how much to bolus: if no response, do not be afraid of giving more (you often need 9-12mg/kg), but be ready to ventilate the animal mechanically.
      (ii) propofol: 3-6mg/kg bolus followed by infusion of 0.4 – 0.8mg/kg/minute. Follow up with a blood gas to check the animal is not hypoventilating. Intubate and ventilate if necessary. In some animals propofol is proconvulsant, but in most it is anticonvulsant. The advantage over pentobarbital is that it should have less cardiovascular and respiratory depressant effects, and recovery is much faster than from a pentobarbital coma.

Once you have got to the anesthesia phase you must monitor:

1) Blood gases to ensure the patient is not hypoventilating. Also, many of these animals can develop aspiration pneumonia and/or non-cardiogenic pulmonary edema.
2) Body temperature.
3) Blood pressure, heart rate and rhythm.
4) Bladder: monitor urine production.
5) Make sure jugular veins are not occluded: preferably put head at 30° from the horizontal.
6) Monitor pupil size and responsiveness: any sign of deteriorating neurologic status, give mannitol, 0.5 – 1g/kg slow iv.

As the animal comes out of the pentobarbital coma, you must make sure that it has adequate blood levels of phenobarbital. Also, recovering animals will often paddle, and it can be difficult to determine whether this is a seizure or just recovery. To differentiate, check the heart rate and try moving or holding the animal. If it isn’t a seizure, the heart rate has not usually increased, and the paddling will slow as you move the animal. If unsure, try a dose of diazepam and see what happens.

REFERENCES