TO SEIZE OR NOT TO SEIZE: TOP 10 THINGS YOU SHOULD KNOW ABOUT SEIZURES

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1. I have a patient that had an “episode.” Do you think it was a seizure?

Seizure: Refers to a sudden, transient, abnormal phenomenon of a motor, sensory, autonomic, or psychic nature resulting from transient dysfunction of part or all of the brain. It is probably more acceptable to call it an epileptic seizure.

Epilepsy: A disorder of the brain characterized by recurring, unpredictable seizures.

How do you determine if a patient had an epileptic seizure or not? A complete history and thorough description of the episode are essential when determining if the patient had an epileptic seizure or not. The following questions can help determine if the episode was an epileptic seizure.

• Was there a trigger? Epileptic seizures have a peracute and unexpected onset and offset. Trigger are extremely rare.
• Was there a pattern to it? Epileptic seizures have 3 phases: pre-ictal, ictus, and post-ictal. The pre-ictal phase is usually not seen. The ictus typically lasts less than 2 minutes. After the ictus, the patient may be normal or have post-ictal signs (pacing, hunger, thirst, aggression, acting blind) that can last seconds to an hour.
• Was the patient conscious during it? Most seizures impair or alter consciousness.
• Was there involuntary motor activity or abnormal behaviors? Epileptic seizures usually result in voluntary motor activity (paddling, tonic-clonic movements, muscle twitching) and abnormal behaviors (fly-biting, vocalization, running in circles, aggression).
• Was there an autonomic sign? Epileptic seizures may result in urination, defecation, salivation.

Paroxysmal Events That Mimic a Seizure

<table>
<thead>
<tr>
<th>Paroxysmal Event</th>
<th>Differentiation Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>• Often associated with excitement or exercise</td>
</tr>
<tr>
<td></td>
<td>• Partial or complete loss of consciousness</td>
</tr>
<tr>
<td></td>
<td>• No motor activity</td>
</tr>
<tr>
<td></td>
<td>• No post-ictal phase</td>
</tr>
<tr>
<td>Vestibular attack</td>
<td>• Associated with vestibular signs (head tilt, nystagmus)</td>
</tr>
<tr>
<td></td>
<td>• No loss of consciousness</td>
</tr>
</tbody>
</table>
### Paroxysmal Event Differentiation Criteria

<table>
<thead>
<tr>
<th>Paroxysmal Event</th>
<th>Differentiation Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy/Cataplexy</td>
<td>• Loss of consciousness&lt;br&gt;• Transient flaccid paralysis&lt;br&gt;• Can be precipitated by excitement or feeding&lt;br&gt;• No post-ictal phase</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>• Exercise-induced weakness&lt;br&gt;• Normal mental status&lt;br&gt;• No post-ictal phase</td>
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</tbody>
</table>

2. **What are the most common diseases that cause seizures?**

Age of seizure onset is one of the easiest ways to classify diseases that cause seizure.

<table>
<thead>
<tr>
<th>Younger than 1 Year Old</th>
<th>Between 1-5 Years Old</th>
<th>Older than 5 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative diseases</td>
<td>Idiopathic epilepsy</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Developmental</td>
<td>Metabolic/Endocrine</td>
<td>Metabolic/Endocrine</td>
</tr>
<tr>
<td>• Hydrocephalus</td>
<td>• Electrolyte disorders</td>
<td>• Electrolyte disorders</td>
</tr>
<tr>
<td>• Chiari-like malformation</td>
<td>• Hepatic disease</td>
<td>• Hepatic disease</td>
</tr>
<tr>
<td>• Hypoxic injury</td>
<td>• Renal disease</td>
<td>• Renal disease</td>
</tr>
<tr>
<td>• Hypoglycemia</td>
<td>• Hypoglycemia</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Inflammatory</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>• Portosystemic shunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td>Toxic</td>
<td>Toxic</td>
</tr>
<tr>
<td>• Lead</td>
<td>Trauma</td>
<td>Trauma</td>
</tr>
<tr>
<td>• Organophosphates</td>
<td>Vascular</td>
<td>Vascular</td>
</tr>
<tr>
<td>• Strychnine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Seizures that occur after feeding are more likely to be associated with hepatic disease. Seizures that occur during fasting, exercise, or activity are more likely to be associated with hypoglycemia.

3. **What anticonvulsant do you use first to treat seizures in dogs?**

Phenobarbital is the first drug of choice for treating seizures in dogs because it’s inexpensive and effective. It has an approximately 80% success rate in controlling seizures in epileptic dogs. The starting dose is 2.5 mg/kg PO BID.
Phenobarbital has a half-life of about 32-89 hours, so a steady-state serum concentration is achieved in about 10-14 days. The phenobarbital serum concentration can be measured once a steady-state is reached.

Side effects are commonly observed with phenobarbital. Dogs may be temporarily sedate and groggy for 2-3 weeks after starting phenobarbital because the liver has to become more efficient at metabolizing the drug. It is important to inform the client that this can occur when starting a patient on phenobarbital. Other side effects include polydipsia, polyuria, and polyphagia. The serum alkaline phosphatase (ALP) and serum alanine transaminase (ALT) will increase in many dogs taking phenobarbital. Hepatotoxicity can occur but is usually associated with chronic serum concentration above 35ug/ml. Idiosyncratic blood cell dyscrasias (anemia, thrombocytopenia, leukopenia) can also occur but are rare.

**4. When should the phenobarbital level (also referred to as phenobarbital serum concentration) be checked and what level do you recommend?**

The phenobarbital serum concentration should be checked 2 weeks after starting the drug and 2 weeks after any dose change.

The initial phenobarbital serum concentration should be between 25-30 ug/mL (target range); most of the patients we manage for seizures require a concentration in this range to adequately control their seizures. If a patient has a serum concentration that is not in this range, the dose should be adjusted (increased or decreased) to obtain a serum concentration in this range. If the serum concentration is in the target range, continue the current dose – there is no need to adjust it!

Once a patient’s seizures are controlled, the serum phenobarbital concentration should be checked every 6 months to ensure that it is not above 35 ug/mL. Prolonged serum concentrations above 35 ug/mL increase the risk of hepatotoxicity. This is important because national laboratories report normal phenobarbital concentrations from 10-40 ug/mL. A complete blood count, chemistry panel, and bile acids should also be done every 6 months to monitor for idiosyncratic blood cell dyscrasias and hepatotoxicity.

Michigan State University reports normal phenobarbital concentrations from 60-130 umol/L. To covert umol/L to ug/ml, you simply multiply MSU’s level by 0.232.

**5. What anticonvulsants do you use as an add-on to phenobarbital?**

Several factors should be considered when deciding which medication to use as a second anticonvulsant: 1) Cause of the seizures, 2) Presence of metabolic disease, 3) Owner compliance, 4) Side effects, and 5) Cost.

Zonisamide, levetiracetam, and bromide are used as add-on anticonvulsants to phenobarbital. Zonisamide is used more commonly because it is given every 12 hours. Levetiracetam needs to
be given every 8 hours, which can be difficult for most clients. Both drugs have a high margin of safety, are well tolerated, and have minimal side effects. If a patient’s seizures are well controlled after starting zonisamide or levetiracetam, you can attempt to wean them off Phenobarbital. While potassium bromide can be used as a second anticonvulsant, we often use it as an add-on to zonisamide or levetiracetam because of its long half-life, side effects, dietary restrictions, and cost.

**Zonisamide**

*Dose:* 5 mg/kg PO BID as monotherapy; 10 mg/kg PO BID as add-on therapy to phenobarbital.

*Safety:* Very safe. Most is excreted unchanged in urine although some hepatic metabolism occurs. Is a sulphonamide-based drug, so you should monitor for side effects associated with sulphonamides (allergic reactions, arthropathy, anemia, thrombocytopenia, hepatopathy, skin reactions).

*Side Effects:* Minimal. Mild ataxia and sedation may occur after initiating therapy. Vomiting and loss of appetite have been reported in some dogs.

*Monitoring:* The half-life is 17 hours so a steady-state is reached in 3-4 days. A serum concentration should be checked 1-2 weeks after starting it. The desired therapeutic range is 10-40 ug/mL.

**Levetiracetam**

*Dose:* A starting dose of 10-20 mg/kg PO BID is gradually increase to 20 mg/kg TID. Suggested that extended release formulation has a half-life in excess of 7 hours in dogs which may allow for once or twice daily administration.

*Safety:* Well absorbed and is rapidly metabolized. Predominately renally excreted (>80%). Wide fluctuations of drug metabolism in dogs. Use caution in cats with renal disease.

*Side Effects:* Well tolerated with sedation noted as the most common adverse effect.

*Monitoring:* Half-life is 2-4 hours so a serum steady-state is achieved in 1-2 days. Therapeutic range is not well defined; however, in humans the therapeutic concentration is 5-45 ug/mL. Drug monitoring helps establish the metabolism pattern of the individual patient.

**Potassium Bromide**

*Maintenance Dose:* 20-40 mg/kg PO every 24 hours or divided; give with food to avoid nausea.

*Safety:* Not metabolized by the liver. Excreted in the urine. Avoid in patients with renal disease. Diet must be consistent.

*Side Effects:* Polyphagia, Polydipsia, Polyuria, Pancreatitis, Megacystis, Megacoeles; when used with phenobarbital may see sedation and ataxia.

*Monitoring:* The half-life is 25 days so a serum steady-state reached in 120 days. Therapeutic range is 1000-3000 ug/mL. A serum concentrations is checked 4 months after starting drug.
6. Should I check a trough or peak phenobarbital level?
We recommend checking a trough phenobarbital level.

A study determined there was no clinically significant impact of blood collection timing on the phenobarbital serum concentrations in the majority of epileptic dogs (90%). However, blood collection timing was clinically significant in a small number of epileptic dogs (10%). Note that these were epileptic patients.

Why do we recommend a trough phenobarbital level?
1. Not all dogs with seizures have epilepsy as the underlying cause.
2. You cannot identify the small percentage of epileptics where sample timing is clinically significant.

The trough level is when a drug’s blood concentration is at its lowest. Checking a trough level allows you to make sure that the blood concentration is not falling below the recommended therapeutic range.

A trough phenobarbital level is done by collecting a blood sample immediately before administering the next phenobarbital dose. This can be difficult for some owners because of scheduling. If a trough phenobarbital level cannot be done because of an owner’s schedule, a blood sample can be collected at any time. The ideal patient would be epileptic, have good seizure control, and have normal liver function. You a should also keep in mind that trough levels may need to be done if you are having a hard time controlling the seizures.

Serum separator tubes should be avoided when submitting blood for a phenobarbital level. The silicone in the serum separator tube will bind phenobarbital and give a falsely lower phenobarbital level.

7. How do I adjust the phenobarbital dose after I have checked the blood level?
A low phenobarbital serum concentration is one of the most common causes of poor seizure control. Because phenobarbital metabolism varies among patients, serum concentrations vary among patients taking the same oral phenobarbital dose. Therefore, serum concentrations should be checked to help determine if the initial dose achieves a therapeutic serum concentration. The serum concentration will also guide dose changes.

Serum concentrations should be measured once steady-state is achieved. For phenobarbital this is about 2 weeks; therefore, a blood level should be checked 2 weeks after starting the drug or 2 weeks after any dosage change.

So how do you adjust the dose? Because phenobarbital is cleared by first order kinetics, a dosage change (increase or decrease) should result in a proportional change (increase or decrease) in the serum concentration. This allows for a simple proportion equation which can be used to adjust the phenobarbital dose.
To determine the New Dose, you multiply the Target Serum Concentration by the Current Dose, and then divide by the Current Serum Concentration.

The initial Target Serum Concentration is 25-30 ug/mL. Some patients can be successfully managed with serum concentrations below the target range, while others may have undesirable side effects at serum concentrations within the target range. Treatment should always be individualized.

8. When should I decrease the phenobarbital dose or wean a patient off phenobarbital, and how do I do this?

There are several reasons to decrease the phenobarbital dose or wean a patient off phenobarbital:

1. Patient is seizure-free for one year
2. Side effects of phenobarbital are affecting patient’s quality of life (polyuria, polydypsia, polyphagia, ataxia)
3. Patient develops liver disease
4. Patient develops an idiosyncratic blood cell dyscrasia
5. Patient is being switched from phenobarbital to another anticonvulsant

How do you wean a patient off phenobarbital?

There is no set rule for how to wean a patient off phenobarbital. The key is to slowly wean them off rather than stopping it abruptly. Stopping phenobarbital abruptly could result in rebound (withdrawal) seizures. Most patients can be safely weaned off phenobarbital over a 3-6 month period by decreasing the dose 10-20% every 2 weeks. Ideally, serum phenobarbital concentrations should be checked every month after weaning starts. Phenobarbital can be safely stopped once the serum concentration reaches 10 ug/mL.

The phenobarbital dose can be decreased more rapidly in patients that develop severe hepatotoxicity from phenobarbital. In this situation, the dose can be reduced by as much as 25% a week, or in rare instances stopped abruptly.

9. Which anti-convulsants are recommended to treat seizures in cats?

Phenobarbital remains the drug of choice for treating seizures in cats. It is well tolerated, safe, and predictable.

**Phenobarbital**

*Dose:* Starting dose is 2.5 mg/kg PO BID.

*Side Effects:* Sedation, excessive thirst and urination, and incoordination occasionally occur.

   Facial pruritis, generalized pruritis with distal limb edema, thrombocytopenia, and
leukopenia are also reported side effects of phenobarbital in cats. Hepatotoxicity is rarely reported in cats.

**Monitoring**: The target serum concentration is 25-30 ug/mL, although lower levels may be necessary in some cats that become too sedate. Levels should be checked 2 weeks after starting, 2 weeks after any dosage change, and every 6 months.

**Drugs Used as an Add-on to Phenobarbital**

*Levetiracetam*: 20 mg/kg PO TID; no hepatic metabolism; side effects are rare.

*Topiramate*: Start with ½ of a 15 mg capsule SID mixed in food. Some cats require an entire capsule. Can gradually increase dose to a 25 mg capsule BID (cheaper to have the owners quarter a 100 mg tab). No studies to document safety of this drug; we have used it in a few cases with no obvious side effects.

*Valium*: 0.5 - 2.0 mg/kg PO BID-TID; acute hepatic necrosis can occur so liver function should be evaluated one week and one month after starting this drug, then every 4-6 months.

*Gabapentin*: 5 - 10 mg/kg PO BID. Side effects rare.

Bromide should not be used in cats because it can cause pneumonitis. It is an idiosyncratic, asthma-like condition characterized by a cough and a bronchial pattern on chest X-rays. Signs typically resolve within 1-2 weeks after stopping the medication.

**10. What diagnostic tests should I perform before I refer a patient with seizures?**

Several tests should be included in the minimum diagnostic database for any patient with a history of seizures. Most of these tests can be done in-house prior to referral. Some tests should be included in the minimum diagnostic database depending on the patient’s age and species. These tests will help screen for several structural and metabolic diseases that can cause seizures.

**Minimum Diagnostic Database**

- Complete Blood Count (CBC)
- Chemistry
- Electrolytes
- Blood pressure
- Urinalysis
- Chest radiographs
- Cats: FeLV, FIV, Toxoplasmosis

**Additional Testing Based on Upon Age**

- Bile acids (patients <1 year of age or those suspected of having hepatic disease)
- Complete thyroid panel (older dogs or those suspected of having thyroid disease)
- Toxins (history of exposure to lead, organophosphates, or ethylene glycol)
Extra Questions:

11. What behavioral changes should trigger a neurology referral?
While behavioral changes can be seen with many diseases, there are certain behavioral changes that a patient may exhibit with a structural cerebral lesion (ie. brain tumor, encephalitis). These behaviors should trigger a neurology referral, especially when the patient has a history of seizures. An owner may complain of one or a combination of the following behaviors when their pet has a cerebral lesion:

- Pacing, circling, or wandering aimlessly through house
- Head pressing or staring in space
- Getting stuck in corners or behind furniture (behind door, between tub and toilet)
- Reverse does not work; cannot back up
- Changes in sleeping pattern (up at night, sleeps during the day); sleeps in different places
- Getting lost in house
- Urinating and/or defecating in house
- Not as social

12. When should seizures be treated with anticonvulsants?
- The animal has more than 1 seizure in 8 week period
- The initial seizures are clusters or status epilepticus
- If there is a structural lesion present (ie. tumor, encephalitis)
- Seizures begin within 1 week of head trauma