Approach to Seizure Management FAQ

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INTRODUCTION

There are a lot of resources about seizure management. But there are still questions that often come up that are not well addressed in many of those resources. Hopefully, this FAQ will help fill in some of those gaps.

What should be considered when choosing an anticonvulsant for a patient with a history of seizures?

Several factors go into determining the best initial anticonvulsant for a dog or cat with seizures. Some of these are medical, others are practical.

- **Frequency/severity of seizures**. Do you need to establish control immediately, or are the seizures infrequent enough that you can go more slowly? Anticonvulsants, like all other drugs, require time to get to steady-state concentration. Some do so much faster than others. If you don't have time to lose, starting an anticonvulsant with a short time to steady-state concentration will improve the likelihood of rapidly controlling the seizures.
- **Comorbidities**
    - If you are managing an obese dog, you might consider avoiding phenobarbital or bromide as these anticonvulsants will cause polyphagia and weight gain.
    - If you are managing a dog with weakness, you might consider avoiding the combination of phenobarbital and bromide, which can exacerbate the weakness and ataxia.
    - If you are managing a dog with inappetence, consider avoiding zonisamide, which can cause anorexia at higher doses.
    - Border collies have about a 24% incidence of a single nucleotide substitution in the MDR1/ABCB1 gene associated with resistance to phenobarbital therapy which may explain why it is often a breed associated with refractory epilepsy. In this breed, phenobarbital might not be the anticonvulsant of first choice. Other collie breeds can also carry this mutation. Note, this mutation in this cotransporter is different from the mutation (a 4 base pair deletion) that

results in a loss of function and is responsible for ivermectin toxicity (and other drug toxicities). In other breeds known to have a high incidence of refractory epilepsy (German shepherd, Australian shepherd, Bull Terrier), phenobarbital is often the best first choice antiepileptic. Some neurologists recommend initiating anticonvulsant therapy with two anticonvulsants in breeds known to have a high incidence of refractory epilepsy.

- **Hepatic function/renal function**. Are the organs that metabolize or excrete the anticonvulsants normal or impaired? Sometimes, bile acid concentrations need to be evaluated to determine if liver function is normal or impaired.
- **Frequency of administration**. A drug that requires three-times-a-day dosing can often be problematic for clients. Strict compliance is paramount for good seizure control. If q8 hour dosing is not possible, consider drugs that require less frequent dosing.
- **Are the clients able to do regular follow-up monitoring?** More monitoring is recommended for zonisamide and phenobarbital than other anticonvulsants.
- **Cost of medication**. This can be a significant factor for some clients. Costco pharmacy has historically been very competitive on drug prices and membership is not required to use the pharmacy, so it may be helpful to have your client compare prices at different pharmacies.

How do I evaluate efficacy of an anticonvulsant?

This would seem pretty simple – record the seizure frequency before administering the anticonvulsant and then again after steady-state concentrations have been achieved. However, in reality, it's more complicated than this. Why? Because seizures are not consistent and predictable events. Neurologists recognize that seizures either have festivals or famines – dogs can go through periods with multiple seizures, and then be seizure-free for equally long periods. Therefore, unless the seizure activity has been completely abolished, or you have monitored seizure activity for 6-8 months, it might be difficult to truly determine if a new anticonvulsant is working. A rule of thumb for evaluating anticonvulsant efficacy is to determine the frequency prior to the therapy and then assess for at least 3 times that long after the drug reaches steady state. A reasonable expectation would be at least a 50% longer duration between seizures (seizure-free interval). For example, a dog that has seizures once a month on average would be monitored for at least 3 months after instituting therapy, and we would expect a seizure-free interval of at least 6 weeks.

The best way to determine efficacy is for the ***client to keep a calendar record of seizures*** including the date, duration of the seizure(s), whether or not more than one seizure occurred in a 24-hour period (cluster), and the duration and severity of post-ictal signs. This detailed tracking will allow thorough evaluation of improvement following the initiation, change in dose, and change in administration frequency or addition of other anticonvulsant medications.

What is a steady state concentration?

Steady-state concentrations are those at which equilibrium has been established between drug dosing and drug metabolism/excretion. This results in a relatively uniform concentration of drug. Most drugs reach steady-state concentrations after approximately 5 elimination half-lives.

Below are the times taken to reach steady state concentrations for some of the more commonly prescribed anticonvulsants:

- Bromide – 4 months
- Phenobarbital – 2 weeks
- Zonisamide – 2 weeks
- Levetiracetam – rapidly acting, but half-life is too short to ever reach steady state in dogs or cats.

More details about various anticonvulsant drugs can be found here.

How long should a patient be on an anticonvulsant before evaluating efficacy and checking drug concentrations?

Efficacy and serum or plasma concentrations should be checked once steady state concentrations have been achieved (i.e., after at least 5 half-lives). This obviously varies from drug to drug. For example, phenobarbital and zonisamide achieve steady state after 2 weeks; levetiracetam has a half-life that is too short in dogs to really achieve steady-state concentrations, so most neurologists suggest monitoring after 1 week. See above for assessing efficacy; with bromide, a drug level is recommended at 1 month at which time the level will be about 50% of the level at steady state (4 months) in order to allow time for adjustment if the targeted level is unlikely to be achieved.

Remember to give the same amount of time to reach steady state after a dose change before checking the new level.

When is it time to add another anticonvulsant in a poorly controlled seizure patient?

This FAQ addresses several issues about adjusting anticonvulsant drugs (mostly phenobarbital and potassium bromide). However, when should they be adjusted?

Refractory epilepsy or other seizure conditions can be frustrating and difficult to manage. Most neurologists define "refractory epilepsy" as epilepsy in which adequate seizure control has not been achieved with at least 2 anticonvulsants administered simultaneously at maximum safe/tolerable drug levels.

While many dogs and cats respond to single anticonvulsants (monotherapy), others might require additional anticonvulsants to improve seizure control. Neurologists generally combine anticonvulsants if the owner and veterinarian feel the first-choice drug has not resulted in adequate seizure control at maximum safe/tolerable drug concentrations.

If seizures are not controlled, additional drugs should be considered when:

- Maximum safe drug concentrations of the anticonvulsant have been reached (these are reasonably established for phenobarbital and potassium bromide)
    - For a drug where the therapeutic drug concentrations for the dog and cat are not available (e.g., zonisamide, levetiracetam), dose increases may be made if necessary, until the patient experiences intolerable side effects. If higher doses do result in adequate seizure control, then performing a drug level at that point will provide information on the therapeutic drug level for that patient.
- Side effects (sedation, ataxia, anorexia etc.) are considered intolerable regardless of the dose.
- Adverse clinical signs develop.
- Cluster seizures are occurring. In this case, rapidly acting anticonvulsants, including rectal diazepam, intranasal midazolam or lorazepam, or a short course of oral levetiracetam, can be prescribed in addition to making adjustments to long term anticonvulsant medication.
- Status epilepticus has occurred. Nasal midazolam or rectal diazepam have also been used to help control status epilepticus.
- Post-ictal behavior is either life-threatening to the patient or dangerous to the owner and their family.

Are there interactions between anticonvulsants that I should know or worry about?

Yes. Phenobarbital will increase the metabolism of both zonisamide and levetiracetam. Therefore, consider using high doses of these drugs if combined with phenobarbital.

Phenobarbital and bromide when used concomitantly often cause pelvic limb weakness in the dog as well as increased PU/PD/PP.

Which drugs are safest for use in a dog with hepatic dysfunction?

Bromide and levetiracetam, as they are not metabolized by the liver.

Gabapentin does not have a very good track record as an anticonvulsant in veterinary patients, but it is not metabolized by the liver.

If my patient has been seizure-free for some time and is otherwise healthy and doing well, when may I consider weaning off anticonvulsant medication entirely?

This is a dilemma faced by most clinicians at some point – a dog or cat with seizures was treated with an anticonvulsant, and it seemed to have worked miraculously – the seizures resolved completely. Should you stop the anticonvulsant medications? What's the risk? What is the best way to do this? If the dog or cat has been completely seizure-free, shows no neurological signs for at least a year after initiating anticonvulsant therapy, and is otherwise healthy, you could consider weaning them off the anticonvulsant medication.

However, you should consider the underlying cause of the seizure if known. For example, you might be more reluctant to wean off an anticonvulsant prescribed in a dog with a malformation such as hydrocephalus than an idiopathic epileptic, or dog with an infarct.

If the patient's seizures have been difficult to control in the past, weaning off an anticonvulsant can be riskier than in a patient whose seizures were easy to control on the initial anticonvulsant.

My patient has been well-controlled, but has developed medical issues or intolerable side effects. What do I do?

If the dog or cat has ***medical issues that preclude continuing*** with the anticonvulsant, you will likely need to stop that drug and initiate treatment with another anticonvulsant (or anticonvulsants). For example, if a dog develops an idiosyncratic, severe, acute hepatopathy on zonisamide, you would stop the zonisamide and start bromide with levetiracetam. Because bromide will take 4 months to reach steady state unless loaded and loading can often cause severe sedation for several days, adding levetiracetam which acts very rapidly may prevent seizures while bromide reaches steady state.

Similarly, if the dog develops a severe clinical hepatopathy or anemia with phenobarbital administration, you would stop the phenobarbital immediately, and start bromide and levetiracetam both of which are not metabolized by the liver.

If the dog or cat experiences side effects that the owner finds intolerable, such as severe sedation, polyuria/polydipsia, which are commonly seen with phenobarbital administration, a different anticonvulsant may be added and the phenobarbital weaned more slowly once the new anticonvulsant has reached steady state. Alternatively, zonisamide could be added and once steady state has been reached (2 weeks) then the dose of the phenobarbital could be decreased and continued at the lower dose provided that seizures continue to be well controlled and the undesirable side effects resolve.

What is "good" seizure control?

How do I define "good" or adequate seizure control?

Ideal seizure control is no seizures at all and a patient that is not experiencing any adverse side effects from the medication. Sadly, it can be difficult to achieve this. Therefore, a rule of thumb is satisfactory seizure control can be defined as the point at which, in the opinion of the owner, the seizures are not interfering in the quality of life for their pet. If the owner is willing to work toward complete seizure control, following the steps above will improve the chances of achieving that goal.
