

Thwarting Life Ending Seizure With Acute and Chronic Antiepileptic Drug Therapy William Bush, VMD, DACVIM (Neurology)

Introduction

Optimal management of seizure disorders is important because seizures are common, potentially life threatening, and very upsetting to the other family members. There are several important questions that a veterinarian must ask during every seizure evaluation. One, is the described or perhaps videotaped event actually seizure. Two, is there an underlying genetic, structural or metabolic cause that can be diagnosed and treated more specifically than just treating the symptom of seizure. Three, when and how should I start treatment an antiepileptic drug (AED).

Treatment Challenges

About 30% of epileptic dogs will be refractory or drug resistant. There are variable definitions for this but many dogs continue to have seizure despite having been on more than one AED with trough serum concentrations in the reference range. Cluster seizure (CS) is defined as more than 1 seizure within 24 hours, and status epilepticus (SE) is defined as a 5 minute or longer seizure, 2 seizures without becoming normal in between or seizing at presentation. These are common problems in dogs with idiopathic epilepsy (genetic, unknown cause) with reported rates of CS at 41-94% and SE at 53-59%. Furthermore, in the Border Collie the average life expectancy after the first seizure is 2 years with cluster seizure and status epilepticus being significant risk factors for euthanasia. Therefore the veterinarian often needs to develop a treatment plan for maintenance AED therapy, switching / transitioning AED therapy, and at home and in hospital treatments for cluster seizure (CS) and status epilepticus (CS).

When to start an AED

AED should be initiated when there is a structural cause for the seizure, severe first seizure or post-ictal period or owner's preference is to reduce the chance of another seizure. When the seizures are sporadic and likely from genetic or unknown causes then I would recommend starting an AED after 1 or 2 seizures in 6 to 12 months. The rationale is four-fold. One, AED likely reduces the chance of a life-threatening seizure or SE. Secondly, there is very good experimental and some clinical evidence in people to suggest that having a seizure sets-up or facilitates connections in the brain that reduce the seizure threshold. In other words, every seizure can make it a little easier to have another seizure. We know that about 1/3 of veterinary patients with primary epilepsy are difficult to control and delayed treatment may allow a particular patient to be in this category. Thirdly, a recent study surveying owners of dogs with seizure revealed, not surprisingly, that the most acceptable seizure frequency was not once per month, but no seizure. Another study of dogs on bromide or/and phenobarbital found owners reasonably satisfied with seizures less often than every 3 months. Owners have come to the veterinarian not to be told seizures are harmless and that 1 seizure per a month is acceptable, but to have the seizure disorder treated with the goal being no more seizure. Lastly, the balance between side-effect, risk of organ failure, ease of administration and cost vs. efficacy will determine when an AED is applied. Recent, popular AEDs like Zonisamide and Levetiracetam have few side-effects, little risk, low cost in generic form and can be given twice a day. These medications have been shown to be effective as add-on medications and clinical experience in human and veterinary patients suggest they are effective for monotherapy as well.

Prophylactic AED therapy

In our clinic, patients with lesions from tumor or encephalitis in the cerebrum and sometimes thalamus are often placed on one of the newer AED to try to prevent a first seizure. The perception of benefit in reducing the chance of a seizure is thought to outweigh risks, cost, side-effect and inconvenience of giving AED.

Maintenance Therapy

Maintenance therapy is the application of an AED on a daily basis to reduce or eliminate seizures. There are no placebo controlled or even crossover studies done in veterinary medicine to determine the effectiveness or side-effects of a sole AED (monotherapy) for this purpose.. There have been studies to compare efficacy and side-effect of the traditional AEDs: phenobarbital and bromide, but not with a cross-over design. Multiple studies have been conducted where a newer generation AED (Pregabalin,

Levetiracetam, Zonisamide, Topiramate) have been added-on to traditional AED phenobarbital therapy resulting in at least a 50% reduction in seizure frequency. However, when Levetiracetam was studied as an add-on to phenobarbital and bromide in a placebo controlled, randomized, crossover design, a significant reduction in seizure frequency was not observed but the quality of life was thought better on Levetiracetam relative to placebo. Regardless, when and what AED to apply in the clinical setting remains uncertain or controversial. Some reasonable guidelines for seizure management are to use one medication at a time, determine serum concentrations prior to adding-on or abandoning an AED and pick medications with best efficacy to side-effect ratio. Table 2 is a summary of the AED that are used in our clinic.

Placebo effect

When there was a meta-analysis of three prospective, placebo controlled AED studies it was noted that among the 28 total dogs that 79% had fewer seizure and 29% had fewer than 50% while being treated with placebo. For the 3 trials evaluated, the average reduction in seizures during placebo administration relative to baseline was 26%. The authors concluded their findings were important because open label studies in dogs that aim to assess efficacy of antiepileptic drugs might inadvertently overstate their results and that there is a need for more placebo-controlled trials in veterinary medicine.

When to Change AED

Side effects and lack of efficacy can prompt the need to change AEDs. Studies show that only about 70% of dogs are well controlled on an AED and fewer than half of the dogs on phenobarbital and/or bromide are seizure-free without adverse medication related side-effects. Treating with multiple AED may be beneficial because of broader range of mechanisms and synergy, however side-effects can be additive and determining which AED is effective if difficult when using multiple AED. Therefore AEDs often need to be switched instead of added.

Transitioning AED

Abrupt cessation or missed doses of AED is a common cause of seizure and SE in humans. This is likely less of a concern in dogs – only 6% of SE cases in one study resulted from low AED. Regardless, tapering the dose prior to stopping is recommended and the risk of seizure can be further reduced if at least one AED is maintained in the therapeutic range during transition. Generally I recommend adding on the new AED for 1 week then in the following 5 days reduce the dose of the old AED by 50%, then in the following 5 days reduce the frequency of old AED to once a day and then stop old AED. If marked sedation, ataxia or weakness ensue in the first week then the taper of the old AED or just the stopping is recommended. If there is a marked increase in seizure frequency or severity on the new AED then a return to the former AED and/or substitution / addition of a new, different AED is recommended.

Rescue or Pulse AED Therapy – Oral Therapy

Additional or different, oral or parental AED therapy to control cluster seizure or status epilepticus is called rescue therapy. Oral rescue therapy is appropriate if time to next seizure is an hour or greater which will give time for AED to start to reach a useful serum concentration, for example Levetiracetam takes about 81 minutes to reach maximal serum concentration. A recent double-blind, placebo controlled, crossover pilot study of 6 outpatient dogs with idiopathic epilepsy and cluster seizure being treated with maintenance doses of bromide and phenobarbital was performed with Levetiracetam 30 mg/kg, PO, Q8 h (or placebo) given after first seizure and for 24 hours after last seizure. There were statistically fewer cluster seizure in the study group and the authors concluded Levetiracetam pulse therapy for cluster seizure is probably effective. Because most patients are already on Levetiracetam or Zonisamide, the author often uses Gabapentin (10-30 mg/kg, Q8 H, and/or Clorazepate (1/2 to 2 mg/kg, Q 8 h) for pulse therapy – given after the first seizure and continued for 24 hours after the last seizure. Phenobarbital is used commonly for CS and SE and is given until seizure stop and then stopped – the dose is 6-10 mg/kg after every seizure up to total dose of 40 mg/kg. Acepromazine at 0.5 to 1 mg/kg, PO, up to every 6 hours, can be useful to reduce post-ictal confusion and prevent stress-induced seizure. Bromide is avoided for pulse therapy due to side-effects and long elimination half-life. Lastly, Recent EEG evidence suggests from dogs suggest that seizure are not random events and that forecasting seizure is possible. Therefore while therapy can be initiated after a seizure, it can potentially be administered before a seizure, as many owners think they can predict when

a seizure will occur. To discern the side-effects of an AED used for pulse therapy separate from the influence of the post-ictal state or additional maintenance medication, I advise owners to try the novel AED between seizures and before it is used in the rescue scenario.

Parenteral Rescue Therapy

Intranasal, subcutaneous, intramuscular and rectal AED administration have been advocated when patient unable to swallow and/or when rapid cessation of seizure activity is required and intravenous route not available (at home or ambulance therapy). Subcutaneous Levetiracetam 60 mg/kg will reach therapeutic concentrations in 15 minutes or less and last for 7 hours and currently authors at home therapy of choice. The same dose, undiluted can be given as intravenous bolus to rapidly achieve useful serum concentrations without causing any sedation. Intranasal midazolam using a syringe or preferably a mucosal atomized device has been recently shown to be vastly superior to rectal Diazepam solution. Midazolam 0.2 mg/kg intramuscular or intranasal can also be recommended. Phenobarbital is commonly used by the author for CS and SE at 8-10 mg/kg doses up to total doses of 60-70 mg/kg, provided the systolic blood pressure is greater than 90 mmHg. Rectal valium suppository formulations have unfavorable absorption and are not recommended for emergency treatment of seizure.

AED Monitoring

Serum drug concentrations can be monitored for many of the AED – see Table 2. The author will assess serum concentrations when starting a new AED in a difficult to control patient, when toxicity is suspected at a relatively low dose, or before abandoning an AED because there is poor seizure control. Another important consideration is that phenobarbital will increase metabolism of both Levetiracetam and Zonisamide such that the serum concentrations maybe 50% lower than expected. Therefore serum concentrations of these AEDs are recommended whenever they are added-on to phenobarbital. Lastly, since liver, kidney, bone marrow, immune, and urinary calculi problems are possible as a consequence of AED therapy, biochemistry, complete blood cell count, urinalysis and physical examination are recommended at minimum every 6 to 12 months based on AED therapy and patient's needs.

Table 1. Maintenance AED Therapy in Dogs

Drug	Dose	Side Effect Scale	Primary Side Effect	Reported Toxicity / Dysfunction
Levetiracetam*	25-50 mg/kg PO, Q8 h (or Q 12 for extended release)	1	Ataxia, sedation	None
Zonisamide*	5-10 mg/kg PO Q 12 h	2	Decreased eating, ataxia, sedation	Liver, Kidney
Gabapentin	10-30 mg/kg PO Q 8 h	2	Sedation	None
Pregabalin	2-4 mg/kg PO Q 12 H	2	Sedation	None
Phenobarbital*	2-6 mg/kg PO Q 12 H	4	Ataxia, polydipsia, polyphagia, weight gain, polyuria, sedation, weakness	Liver, bone marrow, skin, endocrine
Bromide *	25-50 mg/kg PO Q 24	5	Ataxia, diarrhea, polydipsia, polyphagia, weight gain, sedation, vomiting, weakness	Esophagus, pancreas, stomach, panniculus
Felbamate	10-60 mg/kg PO Q8	1	Tremors (rare)	Liver, bone marrow, lacrimal gland (KCS)
Topiramate	5-10 Mg/kg PO Q 8-12 H	1	Sedation	Urinary calculi
Clorazepate	½ to 2 mg/kg PO Q 12 H	3	Ataxia, sedation, weakness, polyphagia	None

*Indicates serum drug monitoring recommended

Example Pulse or Rescue Therapy Medications

Drug	Route	Dose Mg/Kg	Frequency
Phenobarbital	PO	6-10	O
Keppra Injectable	SC	60	O
Keppra IR	PO	30	T
Midazolam	IN	0.2 - 1.0 mg/kg	O
Midazolam	IM	0.5-2.0	O
Acepromazine	PO	1.0	O
Gabapentin	PO	30	T
Zonisamide	PO	10 mg/kg	B

O – once, no closer than every hour

T – every 8 hours for 24 hours after seizure

B- every 12 hours for 24 hours after seizure

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