Antiepileptic Therapy in Dogs - Fundamentals and Cases

How does success look like?

Outcome in individual patients: impact on seizures

Table 1: Categorization of outcome in individual patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free</td>
<td>Seizures fully controlled</td>
</tr>
<tr>
<td>Seizure reduction</td>
<td>Reduction in seizure frequency</td>
</tr>
<tr>
<td>Seizure relapse</td>
<td>Seizures re-occur</td>
</tr>
<tr>
<td>Term drug-resistant</td>
<td>Seizure response to multiple drug therapies</td>
</tr>
</tbody>
</table>

Evaluate short-term & long-term success.

Term drug-resistant combined with drug information.

Thank you

Marios Charalambous
International Veterinary Epilepsy Task Force

1. International Veterinary Epilepsy Task Force consensus report on epilepsy definition, classification and terminology in companion animals (chaired by Prof. Mette Berendt)
2. International Veterinary Epilepsy Task Force Consensus Proposal: Diagnostic approach to epilepsy in dogs (chaired by Drs. Luisa De Risio and Sofie Bhatti)
3. International Veterinary Epilepsy Task Force current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs (chaired by Prof. Velia-Isabel Hülsmeyer)
5. International Veterinary Epilepsy Task Force Consensus Proposal: Outcome of therapeutic interventions in canine and feline epilepsy (chaired by Profs. Kaspar Matiasek and Martí Pumarola)
6. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol (chaired by Drs. Clare Rusbridge and Sam Long)
7. International Veterinary Epilepsy Task Force recommendations for systematic sampling and processing of brains from epileptic dogs and cats (chaired by Profs. Hans Lohi and Mark Fernando Batters)

ACVIM consensus statement - Panel Members

Scenario

A 5 years old 17 kg German Shepherd intact male dog manifested single generalized tonic-clonic seizures one year ago. The dog is normal in-between the episodes. You wonder what the best treatment would be.

Which drug would you use?

1. Phenobarbitone
2. Imepitoin
3. Potassium bromide
4. Levetiracetam
5. Gabapentin
6. Zonisamide
Which drug would you use first line?

1. Phenobarbitone
2. Imepitoin
3. Potassium bromide
4. Levetiracetam
5. Gabapentin
6. Zonisamide

Scenario

A 5 years old 17 kg German Shepherd intact male dog manifested single generalized tonic-clonic seizures one year ago. In the last two months the dog manifested five episodes. The dog is normal in between the episodes, idiopathic epilepsy is suspected. You wonder what the best treatment would be.

How high is the placebo effect if you are a surgeon or a medic?

Placebo Effect in Canine Epilepsy Trials
K.R. Mofana, D. Zhang, and E.E. Patterson
ACVIM Panel Grade of Recommendations (Level of Evidence) for AED Monotherapy

A (HIGH)  
- Phenobarbital (I)  
- Levetiracetam (I)

B (MODERATE)  
- Bromide (I)  
- Zonisamide (III)  
- Primidone (II)

C (LOW)  
- Levetiracetam (IV)  

D (NO)  
- None

IVETF - Consensus proposal - Choice AED

- In an otherwise healthy dog
  - Start with PB
    - Recurrent single generalized epileptic seizures (E)
    - Status epilepticus (II)
    - Other epilepsy types
  - Start with Levetiracetam
    - Recurrent single generalized epileptic seizures (E)
  - Kbr
    - Add-on

Side effects

When would you check Phenobarbital serum levels for the first time?
1. 2 days
2. 12 days
3. 30 days
4. 90 days
The peak and trough debate

When would you check Phenobarbitone serum levels for the first time?
- 1. 2 days
- 2. 12 days
- 3. 30 days
- 4. 90 days

Phenobarbitone (dog):
- First line treatment
- Dose: 3, 5 mg/kg BD
- Peak serum concentration: 0.8 hours (oral)
- Half life: 20-60 hrs
- Time to steady state: 10-14 days
- Therapeutic range: 20–40 mg/L
- Potential side effects: sedation, PFOA, polyphagia, hepatotoxicity
- Metabolism: liver
- Drug interaction: Can alter serum levels of metabolized drugs
- Obtain plasma level: 10, 20, 40, 100, 360 A.U., then q 4 D.

Loading dosage if indicated:
- 10–20 mg/kg total dose with a phasoch (equal dose 0, 6, 12, 18 hrs to effect, i.e. no seizures)

Phenobarbitone

Phenobarbitone (PB)
- Rare but severe (idiosyncratic reactions):
  - Behavioural alterations
  - Immune-mediated neutropenia, thrombocytopenia, anemia
  - Superficial, necrotic dermatitis
  - Idiosyncratic hepatoxic reactions (rapid elevation of ALT and abnormal bile acids)
- Action: stop drug immediately—load with another AED

Withdrawing seizures (drug dependence)
- How to stop?

Comparison of phenobarbitol with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs

Phenobarbitol

Phenobarbitol for the Treatment of Epilepsy in the 21st Century: A Critical Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic range</th>
<th>Half-life</th>
<th>Metabolism</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>20–40 mg/L</td>
<td>20-60 hrs</td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td></td>
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Phenobarbitone (PB)

Phenobarbitone (PB)

Phenobarbitone (PB)

Phenobarbitone (PB)
One month later the dog had 4 seizures.
What do you want to do now?
1. Check serum levels (PB)?
2. Add potassium bromide or another antiepileptic drug?
3. Refer to a neurologist?
4. Repeat the neurological exam?
5. Ask for a video of the seizures?

When should a second AED be started?
- Strict criteria for decision-making strategy on starting a second AED is lacking in veterinary medicine
- Risk factors associated with poorer seizure control include male dogs and prior cluster seizure activity
  - (Packer et al. 2014)
- Factors to consider
  - Selection of an AED with a different mechanism of action
  - Minimizing drug-drug interactions, avoiding additive toxicity
  - Identification of risk-benefit of polytherapy versus quality of life

*ACVIM Panel Recommendations:*
- Documentation of appropriate drug and maximal level of first AED for a minimum of 3 months
- >50% increase in seizure frequency over 3 months
- New onset of status epilepticus
- New onset of cluster seizures
- Presence of drug-toxicity

When does safe sailing becomes a titanic experience?

Assessment into the usage of levetiracetam in a canine epilepsy clinic.

Data from different sources indicate that levetiracetam (LEV) and double AED therapy.
ACVIM Panel Grade of Recommendations (Level of Evidence) for Add-On AED Therapy

<table>
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<th>B (MODERATE)</th>
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<tbody>
<tr>
<td>Levetiracetam (II)</td>
<td>Bromide (II)</td>
<td>Zonisamide (III)</td>
<td>Primidone (IV)</td>
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</table>

Potassium bromide – add on/first line (not in cats)

- Potassium bromide (II)
  - Dose: 30-60 mg/kg SID
  - Half-life: 120-180 hours
  - Time to steady state: 10-20 days
  - Therapeutic range: 0.7-1.8 mg/mL for dogs
  - Side effects: vomiting, sedation, weakness, ataxia, tremors
  - Liver: 0.2-0.4 mg/kg SID
  - Loading dosage if indicated: 200 mg/kg equal divided over 6 days + maintenance dose

Potassium bromide – dose adjustment
- Full and down-dose in mg/kg/day = (Desired conc / Actual conc) x current dose

Potassium bromide – dietary effect
- High carbohydrate diets lower serum concentration

Potassium bromide – toxicity (I)
- Seizures, sedation, convulsions, vomiting, diarrhea
- E.g., dogs with renal insufficiency (reduced elimination)
- Action: reduce to enhance renal excretion

Other AEDs

- Levetiracetam
  - 1 clinical study (N = 6) (II)
  - 8/11 dogs with > 50% reduction for 6 months (CP seizures)
- Carbamazepine
  - 2 clinical studies N=25 (III)
  - 11/25 with > 50% reduction for 3 or 4 months
- Topiramate
  - 1 clinical study (n = 40) (III)
  - 7/10 dogs with > 50% reduction for 3 months
- Lamotrigine
  - 1 clinical study (n = 10) (III)
  - 9/10 dogs with > 50% reduction between 6-15 months
- Zonisamide
- Sodium valproate clinical studies
- Primidone
- No clinical studies
In relation to etiology, the new ILAE classification schemes.

The term idiopathic is often considered: a remission of seizures, but with a chance and epistatic and epigenetic influences. Molecular mechanisms, new metabolic disorders have been recognized. However, it is also likely that multifactorial nature of etiology

Accounted for many of the complexities in determining causal factors (the analogy of the river of causal factors from Lennox and Lennox) and provoking causes, to have a separate category of acute symptomatic seizure in its current form should be recognized. The analogy of the reservoir from Lennox and Lennox.

This represents the influence of the two main streams. This represents the analogy of the reservoir from Lennox and Lennox.

Causes may be represented as the sources of a branching streams, there is an independent stream which rises in a lake (the uterus). The outlet is the birth canal and below that are contributing streams: infections [e.g., at B, a viral infection], abnormalities of migration [e.g., at A, a genetic abnormality], etc.

Injuries from trauma at birth or subsequently (focal or general) Foreign bodies Aneurysms Gummata Abscesses Tumors

Sequelae of obscure in

Thrombosis and embolism Atrophy of the brain after trauma Connective tissue formation after trauma Injuries from trauma at birth or subsequently (focal or general) Foreign bodies Aneurysms Gummata Abscesses Tumors


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What next in canine epilepsy research?

Summary and Conclusion

MCTD improves seizure control
- Most dogs showed a reduction in seizure frequency in 30 days when fed as an adjunct to veterinary therapy
- Over the course of 90 days:
  - 71%
  - 48%
  - 14%
- No effect on antiepileptic drug serum levels
- MCTD significantly increases BHB serum levels

A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy

Investigating the short-term effects of medium-chain triglycerides (MCT) supplement on canine epilepsy in drug-non responders

Abbreviations: AED, antiepileptic drug; BHB, β-hydroxybutyrate; MCTD, medium-chain TAG diet