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Neurology Survival Kit 2017 Mini Series

Session Three: Everything you always wanted to know about seizures and paroxysmal dyskinesia

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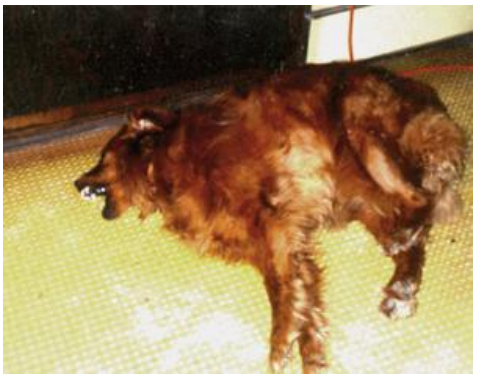


EVERYTHING YOU WANTED TO KNOW ABOUT SEIZURES

INTRODUCTION

There is significant variability and overlap in the clinical presentation for seizures and other types of movement disorders. This translates into the practitioner having to recognize and understand the etiology and treatment of these disorders. Misdiagnosis may lead to inappropriate or ineffective treatments or side effects of those treatments.

Seizure:

The term seizure refers to a sudden attack or recurrence of disease and often implies a dramatic or catastrophic event. The term is therefore non-specific although is often used to describe an epileptic seizure. The term is often used interchangeably with convulsion.

Epileptic seizure:

An epileptic seizure is the physical manifestation of paroxysmal transient disturbance of central nervous system function resulting from excessive and/or hypersynchronous abnormal neuronal activity within the cerebral cortex.

Epilepsy:

Epilepsy is not a specific disease but a chronic condition characterised by recurrent epileptic seizures. A patient having a single epileptic seizure does not have epilepsy, as the seizures are not recurrent.

Movement disorders:

Movement disorders have been greatly under-characterized and rarely describe in veterinary small animal medicine. They can be either persistent or episodic (paroxysmal), and can be broadly defined as overactive (hyperkinetic) or under-active (hypokynetic). The persistent disorders that veterinarians are familiar with and have experience with include tremors, myoclonus, and tetanus.

It is important to recognize that an epileptic seizure is not a disease entity in itself but a clinical sign generally indicative of a forebrain disorder. Movement disorders have different neuroanatomic localization including the brain (basal nuclei, cerebellum, midbrain/rubral), peripheral lower motor neuron and possibly the spinal cord. Not all disorders have a clear cut neuroanatomic basis. The basal nuclei are located below or deep to the cortical grey matter and white matter and surround the thalamus and hypothalamus. The anatomy as well as their connections and physiology of these nuclei are complex and not fully defined. They are comprised of corpus striatum, claustrum and the amygdala.

CLASSIFICATION OF EPILEPTIC SEIZURES

Epileptic seizure types can be classified into two major categories: partial and generalized.

Generalised Seizures:

In dogs, *generalized seizures* (i.e., "grand mal") are the most common type. Generalized seizures have no localized signs and indicate involvement of both cerebral hemispheres. Consciousness is impaired and motor manifestations are bilateral throughout the body. The tonic phase typically lasts about 10-30 seconds in which limbs and neck muscles are stiff, rigid, and extended. This gives way to the clonic phase, in which repetitive limb movements occur. Autonomic discharge is common (e.g., salivation, urination, defecation), as are facial movements (e.g., chewing, twitching).

Absence seizures (i.e., "petit mal") are not well recognized/described in companion animals. The term "petit mal" more commonly is misused to incorrectly refer to partial seizures. True "petit mal" seizures are absence seizures. They are mild, generalized seizures characterized by a sudden, brief loss of consciousness. Either myoclonus or loss of muscle tone may occur. These seizures have a characteristic EEG pattern and respond to different anti-epileptic drugs than other types of seizures.

Partial seizures:

Compared to dogs, cats commonly exhibit partial seizures. This type of seizure indicates abnormal neuronal activity in a localised region of the cerebral hemisphere. Any portion of the body can be involved during a focal seizure depending on the region of the brain affected. The focal nature of this seizure type is associated with a higher incidence of focal intracranial pathologic change in cats. The various forms of partial seizures include:

- *Focal (partial motor) seizures*: unaltered consciousness with asymmetric localised motor signs such as eyelid or facial twitching, clonus of muscle groups of one limb.
- *Psychomotor and complex partial seizures*: psychomotor seizures are typically considered a subtype of complex partial seizures. They manifest as behavioural seizures pattern involving the limbic system which may present as rage, aggression without provocation, fly-catching, running in circles, floor licking, vocalization, tail chasing, etc. Complex partial seizures are cortical seizures similar to the simple partial seizures; however, in complex partial seizures, consciousness is impaired. Other signs are as described above for simple partial seizures.

A seizure may start in a focal region of the brain only to spread throughout both cerebral hemispheres, resulting in a focal seizure with secondary generalization.

CONFIRMATION OF THE EPILEPTIC NATURE OF A PAROXYSMAL EVENT

A paroxysm is defined as a sudden recurrence or worsening of the clinical signs - a spasm or a seizure.

The recognition of an epileptic seizure is essentially based on the owner's description of the event. Although generalised tonic-clonic seizure have a fairly unequivocal description, the recognition of a partial

or psychomotor seizure can pose a real challenge for the clinician. For that reason video footage obtained by the owner of the paroxysmal event can be of tremendous help.

An epileptic seizure can be suspected based on:

- The peracute and unexpected (except cases of “reflex seizures”) onset and offset.
- Stereotypical pattern.
- Presence of involuntary motor activity and/or abnormal mentation and behaviour and/or autonomic signs (salivation, urination and/or defecation).
- Elimination of other paroxysmal events (syncope, acute vestibular attack, myasthenia gravis).

Absolute confirmation of the epileptic nature can only be obtained by observing simultaneously the characteristic EEG changes and physical manifestation of the seizures.

CLASSIFICATION OF UNDERLYING CAUSES OF SEIZURES

The presence of epileptic seizures implies a forebrain disorder. Their causes may originate outside (extra-cranial) or inside (intra-cranial) to the brain. Intra-cranial causes may be further subdivided into functional disorders (where no gross structural changes are evident in the brain) and structural disorders (where there is a gross structural cause within the brain, e.g. a brain tumour or hydrocephalus).

Reactive Seizures: This term is often used to describe seizures resulting from an extra-cranial cause.

Primary Seizures: This term is often used to describe seizures resulting from a functional intra-cranial cause (e.g. Idiopathic Epilepsy).

Secondary Seizures: This term is often used to describe seizures resulting from a structural extra-cranial cause (e.g. brain tumour).

<u>Differential Diagnoses for epileptic seizures</u>

<u>Extra-Cranial Causes of Epileptic Seizures:</u>

Reactive epileptic seizures represent a reaction of the normal brain to a systemic insult or physiological stress. Reactive seizures differ from intra-cranial causes of epileptic seizures, as no primary chronic brain disorder (functional or structural) underlies the seizures.

Secondary changes may be present within the brain, most commonly identified by MRI, occurring as a consequence of severe seizures (irrespective of whether the underlying cause of the seizures originates within or outside the brain). It is important to recognize these secondary changes as such, so as not to misinterpret them as the primary cause of the seizures.

Extra-cranial causes of seizures may originate from outside the body (toxic disorders) or within the body (metabolic disorders). In both instances, the neurological examination may be either normal or abnormal in the inter-ictal period. If neurological deficits are present in the inter-ictal period then they are typically bilaterally symmetrical and non-localising in terms of the anatomic diagnosis.

Common extra-cranial causes of epileptic seizures:

- Hepatic encephalopathy – either due to a porto-systemic shunt (congenital or acquired) or to hepatic cirrhosis. Seizures secondary to hepatic encephalopathy are often associated with an altered mental status and/or behaviour in the inter-ictal period. This evidence of altered mental status and behaviour usually waxes and wanes in severity over time. Other signs of symmetrical forebrain involvement can be observed (central blindness, symmetrical ataxia in all four limbs, head pressing, pacing and aimlessly wandering).
- Hypoglycemia – may cause weakness, syncope or seizures depending on the degree of hypoglycaemia, but more importantly the rate at which the hypoglycemia fluctuates. The most common cause in adult and geriatric dogs is a functional pancreatic tumour (insulinoma) or other insulin-like producing tumour. Less commonly hypoglycaemia may also be associated with (among other causes) severe sepsis, pyometra, hypoadrenocorticism, insulin overdose and hepatic insufficiency.
- Ionic imbalance – hypocalcemia (post-partum or secondary to hypoparathyroidism), hyponatraemia, hyponatraemia, hypomagnesaemia or hyperkalaemia.
- Hyperlipidaemia
- Polycythaemia
- Renal encephalopathy – seizures secondary to renal insufficiency are usually only associated with severe acute or end-stage renal failure.
- Hypothyroidism – whether hypothyroidism is a primary cause of epileptic seizures is subject to considerable controversy. Hypothyroidism has, to a greater or lesser extent, been associated with other neurological disorders including peripheral vestibular disorder, megaoesophagus, laryngeal paralysis, facial paralysis, generalised neuromuscular disorders and encephalopathy. Even if hypothyroidism is not directly associated with seizures the case may be argued that the presence of hypothyroidism may exacerbate pre-existing epileptic seizures. The presence of seizures and in particular phenobarbitone medication may affect the endogenous T4 levels. Other systemic signs, including weight gain, hyperpigmentation, bradycardia, alopecia and lethargy, may be evident in the presence of hypothyroidism.
- Numerous toxins – including carbamates, organophosphates, lead poisoning, ethylene glycol toxicity , methaldehyde (slug bait), strychnine, etc..
- Thiamine deficiency – thiamine deficiency may cause seizures in cats exclusively fed on fresh fish diets (with high dietary levels of thiaminase), fed exclusively on diets where the thiamine has been destroyed (cooked food) or in cats that are anorexic/polyuric. Thiamine has also been reported in dogs in associated with severe seizures. Other clinical signs are invariably present in associated with thiamine deficiency in both cats and dogs, and may include ataxia, dilated and unresponsive pupils, mentation changes, vestibular deficits and decreased gag reflex.

Intra-Cranial Causes of Epileptic Seizures:

Intracranial causes of epileptic seizures can be further divided into functional and structural forebrain disorder.

Common structural intra-cranial causes of epileptic seizures:

Most animals with a structural forebrain disorder demonstrate neurological deficits in the inter-ictal period. These deficits are often asymmetrical and are therefore useful in localising the site of the lesion. The most common localisation is that of a focal forebrain disorder (where the neurological deficits may include ipsilateral circling, contralateral postural reaction deficits, contralateral menace response loss with a normal pupillary light reflex, contralateral abnormal response to stimulation of the nostril, abnormal behaviour), but in some cases evidence of a multifocal neurological disorder may be evident (including the involvement of other cranial nerves, brain regions and even the spinal cord).

There are exceptions to this in that in some cases the lesion causing the seizures lies in an otherwise "silent" region of the brain (causing only seizures but no other localising neurological deficits, most commonly in the olfactory lobe or prefrontal lobes). During the early stages of a slowly enlarging mass only seizures may be evident, but with time other neurological deficits related to the site of the mass will develop.

- Brain tumours - may be primary or secondary (arising from adjacent non-neurological structures and from metastatic spread).

Primary brain tumours may arise from the meninges (e.g. meningioma), choroid plexus (e.g. choroid plexus papillomas), ependymal lining (e.g. ependymomas) or glial cells (e.g. glioma).

Secondary brain tumours may invade or compress the neural tissue after originating from surrounding structures, including the nasal cavity, fibrous connective tissue, bone and muscle. Secondary brain tumours may also arise as a consequence of metastasis from distant sites and as such could lodge anywhere in the brain, meninges, or choroid plexus.

Clinical signs associated with primary or secondary brain tumours may vary depending on the tumour type, location, degree of parenchymal compression, growth rate, inflammatory response and the presence of brain herniation. Seizures are the most common clinical sign in dogs with brain tumours in the forebrain and in many cases (particularly in tumours arising in the olfactory lobe and rostral portion of the frontal lobe) may be the only clinical signs. Other commonly encountered presenting clinical signs are related to forebrain dysfunction. A specific diagnosis for a space-occupying lesion is usually based on demonstrating typical CT or MRI imaging findings, although the only definitive diagnosis is histological evaluation. Treatment options for brain tumours include: a) palliative treatment using anti-inflammatory dosage of prednisolone (starting at 0.5 mg/kg once or twice daily and tapering to alternate day therapy, if the abatement of the clinical signs is maintained on this dose level), b) radiation therapy, c) chemotherapy, and d) surgical resection for accessible tumours.

- Inflammatory (immune-mediated) CNS disease - granulomatous meningo-encephalitis (GME) is the most common form of immune-mediated inflammatory CNS disease. It affects all breeds with a peak onset over a broad age-range from 9 months up to 10 years. There appears to a predisposition in female dogs and in the poodle and terrier breeds. The etiology and pathogenesis are unknown. The lesions consist of a concentric proliferation of inflammatory cells (lymphocytes, plasma cells, and other large mononuclear cells) around blood vessels principally in the brain and/or spinal cord

white matter as well as the meninges. These lesions may coalesce to form a mass that may mimic a space-occupying lesion and compress the CNS parenchyma. The clinical signs reflect the size and location of the lesion(s). Three forms of GME may be distinguished: **focal** (some focal forms of GME are suspected to be primary B-cell lymphoma), **diffuse** or **optic nerve** GME. CSF results usually reveal a mixed mononuclear pleocytosis (but may be normal or consist primarily of neutrophils in acute cases). Although definitive diagnosis can only be made following histological examination (following biopsy or post-mortem), a highly probable diagnosis can be made based on the demonstration of multifocal contrast-enhancing oedematous lesions on MRI examination. Improvement may be evident in some cases following immuno-suppressive dosage of corticosteroid (1 mg/kg twice daily) ± azathioprine (1mg/kg once daily) ± Cytarabine therapy, ± radiation therapy. There is some evidence to suggest that dogs with focal neurological deficits have longer survival times than those with multifocal neurological deficits.

- Head trauma – any head trauma has the potential to cause seizure. The onset of the seizures may be shortly after the insult or after a few weeks to months (as a consequence of a glial scar that could act as an epileptic focus).
- Infectious CNS disease – as for head trauma the onset of the seizures may occur during the period of active infection or the onset may be delayed as a result of a continued inflammatory focus or glial scar. Active infection is usually associated with multifocal, asymmetrical inter-ictal neurological deficits.
- Anomalous – clinical signs are often observed in immature or young adult and are usually non-progressive (excepted congenital hydrocephalus that can sometimes worsen with time).
- Cerebrovascular disease – Previously considered uncommon, cerebrovascular accidents (CVA) are increasingly recognised in dogs or cats with the advance of neuro-imaging. CVA's are characterised clinically by a peracute or acute onset of focal, asymmetrical and non-progressive brain dysfunction. Seizures are, however, not a common finding in CVA's.

Seizures due to functional intra-cranial causes:

The term primary (or idiopathic) epilepsy implies a functional forebrain disorder causing recurrent epileptic seizures with a normal interictal period and no identifiable toxic, metabolic or structural intracranial causes. Idiopathic epilepsy occurs less commonly in cats than dogs. The diagnosis of idiopathic epilepsy is unfortunately a diagnosis of exclusion as there is currently no definitive diagnostic test to confirm the diagnosis.

HOW TO ESTABLISH THE DIFFERENTIAL DIAGNOSIS LIST?

Likely Causes of Seizures Related to Age of Onset
Immature (less than 6 month old) ○ **Porto-systemic shunt** ○ **Toxic causes (e.g. organophosphates)** ○ **Infectious CNS disease (Distemper, Neosporosis, FIP, FeLV)** ○ Malformation ○ Hypoglycemia ○ Head trauma
Young Adult (between 6 months and 6 years old) ○ **IDIOPATHIC EPILEPSY (dogs)** ○ **Inflammatory/infectious CNS disease** ○ Head trauma ○ Metabolic disease ○ Toxic causes (e.g. organophosphates) ○ Neoplasia
Adult (more than 6 year old) ○ **NEOPLASIA** ○ **Metabolic (e.g. hypoglycemia secondary to an insulinoma)** ○ **Inflammatory CNS disease** ○ Head trauma ○ Toxic causes (e.g. organophosphates)

Likely Causes of Seizures Related to Neurological Findings in the Inter-Ictal Period
Normal inter-ictal examination ○ **IDIOPATHIC EPILEPSY** ○ **Structural brain disease (e.g. neoplasia) in 'silent' area of the forebrain** ○ **Early stages of structural brain disease (e.g. neoplasia)** ○ Metabolic disease (clinical signs can wax and wane with the metabolic derangement and may be normal at the time of assessment)
Abnormal inter-ictal examination with symmetrical neurological deficits ○ **Metabolic disease** ○ **Toxic causes (e.g. organophosphates)** ○ Hydrocephalus (congenital or acquired) ○ Midline structural brain disease (e.g. pituitary tumour) ○ (Degenerative disease)
Abnormal inter-ictal examination and asymmetrical neurological deficits ○ Structural brain disease (**neoplasia, inflammation/infection**, previous cranial trauma, malformation)

Most Common Presentation Based on Anatomic Diagnosis
Functional (Intracranial) e.g. Idiopathic Epilepsy ○ Generalized seizures (rarely partial) ○ Initially low frequency ○ Normal neurological examination in the interictal period ○ Normal CSF analysis ○ Normal brain imaging
Structural Intracranial Causes ○ Partial or generalized seizures ○ Variable frequency ○ Neurological deficits in inter-ictal period (except lesions in 'silent' areas of the brain or in early stages of an enlarging mass) ○ Normal or abnormal CSF analysis ○ Usually abnormal brain imaging
Extracranial Causes (Metabolic or Toxic) ○ Generalized seizures ○ Often high frequency ○ Often abnormal neurological examination in the inter-ictal period (diffuse and symmetric deficits – can wax and wane) or during the period preceding the seizure (muscular weakness with hypoglycemia, tremor with hypocalcemia, abnormal mental status and behaviour with hepatic encephalopathy) ○ Abnormal biochemical findings (hypoglycemia, hypocalcemia, uremia, electrolyte imbalance, elevated pre- and post-prandial bile acids) ○ Documented exposure to toxins

CHOICE OF APPROPRIATE DIAGNOSTIC TEST

It would not be unreasonable to make a diagnosis of Idiopathic Epilepsy in a dog (and to a lesser extent a cat) demonstrating:

- The right age and signalment (particularly in a breed with a high incidence of idiopathic epilepsy).
- The presence a normal haematological and biochemical evaluation.
- History and seizure characteristics consistent with Idiopathic Epilepsy (generalised tonic-clonic seizures from rest and with the seizure onset between one and three years of age – but from 6 months to 6-years is acceptable).
- No abnormalities in the inter-ictal period.

If these cases later developed further clinical signs to suggest an alternative diagnosis or if the seizure control was poor then further investigation would be justified.

Investigation of Suspected Extra-Cranial Causes

- Complete haematology
- Comprehensive biochemistry including pre- and post-prandial bile acids
- Urinalysis
- Total T4 in adult cat suspected of hyperthyroidism, Total T4, Free T4 and endogenous TSH in dogs
- FeLV, FIV tests
- Toxoplasma serology (IgM and IgG), Neospora serology

Investigation of Suspected Extra-Cranial Causes

- Complete haematology
- Comprehensive biochemistry
- Thoracic radiographs
- MRI scan or CT-scan of the brain
- CSF analysis (protein quantification, complete and differential cell count)
- In those case with inflammatory CSF or imaging findings consideration should be give to performing serology for and/or CSF PCR for: distemper virus, coronavirus, Toxoplasmosis, Neosporosis, FeLV and/or FIV.

MAINTENANCE THERAPY FOR EPILEPTIC SEIZURES

Aims of Treatment:

- Reduce the frequency and severity of seizures.
- It is important to explain to the owner that the animal will still seizure despite the therapy (if an animal diagnosed with idiopathic epilepsy has not had an epileptic seizure for more than six months, then you may need to reconsider your diagnosis).

- Minimise potential side effects.
- Minimise the demands made on the owner.

Client Education:

- The therapy for epileptic seizures does not aim at curing the epilepsy but aims at "controlling" it.
- Therapy for epileptic seizures may have side effects that in rare occasion can be worse than the seizures themselves.
- Mild side effects are common when first starting treatment with anti-epileptic drugs.
- Therapeutic effects and side effects are related to the serum levels and not the oral dosage of the anti-epileptic drug.
- Skipping doses or stopping drugs abruptly can precipitate seizures (dependency effect).
- Seizure control may not take immediate effect as a steady serum state is only reached after 5 elimination half-lives (around 2-weeks in phenobarbitone and up to 3-months in potassium bromide).
- Clients must keep accurate record of the date of any witnessed or suspected seizures and must be willing to bring their dog or cat in for periodic examination.
- Clients should seek immediate veterinary care for any seizure lasting longer than 10 minutes or for clusters of seizures without recovery to normal between the seizure episodes.
- Clients should not alter the treatment without veterinary advice.

When to Start Treatment?

There are essentially two schools of thought. Many dogs will have a single seizure episode in their lives, therefore it may not be feasible to treat every dog that seizures. The first school of thought advises treatment of seizures as soon as a dog is diagnosed as having recurrent seizures (i.e. after the second seizure episode). In human medicine it has been demonstrated that early instigation of seizure treatment will result in significantly improved long-term control. This is borne out by experimental evidence (kindling and mirror effects) and a single study in dogs that suggest that early treatment offers better long-term control of the seizures as compared to animals that are allowed to have numerous seizures prior to the onset of treatment. The second school of requires balancing the benefits gained from the introduction of anticonvulsant therapy with the adverse effects caused by the medication and the demands on the owner.

Although largely arbitrary and greatly dependent on owner demands and compliance the following would be a reasonable guide to starting treatment:

- Where more than one seizure occurs per month and/or the owners objects to their frequency.
- If the animal has a very severe seizure or a cluster of seizures, irrespective of the frequency of the seizures or seizure clusters.
- The seizures are increasing in frequency or severity.
- An underlying progressive disorder has been identified as the cause of the seizures.
- Post-ictal signs are objectionable (e.g. aggression).

Initial Anticonvulsant Therapy

Initial treatment of all cases should comprise phenobarbitone (Epiphen™), either as a tablet formulation or a liquid suspension.

Primidone (Mysoline™ oral 250mg tablets) is less suitable but can be considered as an alternative if phenobarbitone is not available. Primidone undergoes hepatic oxidisation to phenobarbitone and phenylethylmalonic acid (PEMA), and although all three of these compounds have anticonvulsant activity, phenobarbitone accounts for 80 to 85%. There is an increased risk of hepatic and behavioural side effects with Primidone; therefore it is advisable to use phenobarbitone. To convert to phenobarbitone from primidone: roughly 250mg of Primidone is equivalent to 60mg of phenobarbitone. It has been suggested that in some cases refractory to phenobarbitone therapy, improved control may be evident with primidone – however is may be more advisable to first try potassium bromide in conjunction with phenobarbitone first, prior to assessing the response to primidone.

Potassium bromide can be used a primary maintenance therapy for epileptic seizures, however it is more commonly used in conjunction with phenobarbitone in cases refractory to phenobarbitone therapy on its own. Consideration should be given to the use of potassium bromide as the sole anticonvulsant medication in cases with evidence of marked hepatic impairment, where the use of phenobarbitone may potentially exacerbate the hepatopathy.

In cats Diazepam can be used as a maintenance anticonvulsant therapy instead of phenobarbitone. Diazepam is not suitable for maintenance therapy in dogs as the duration of effect is too short.

Because of their short elimination half-life in dogs or cats, other anti-epileptic drugs including phenytoin and valproic acid are less suitable as single agents for maintenance therapy.

PHENOBARBITONE

Phenobarbitone (Epiphen™) is the drug of choice for the treatment of epilepsy in dogs. The drug acts by facilitating GABA-mediated synaptic inhibition by binding to barbiturate receptors on the chloride channel complex. Phenobarbitone binding results in higher intracellular concentrations of chloride and hyperpolarization of the resting membrane potential.

- The initial dose is 2 to 3mg/kg BID (i.e. total daily dose of 4 to 6mg/kg).
- Individual dosages are determined by the serum concentration (once the serum concentration has stabilised), not the actual oral dose.

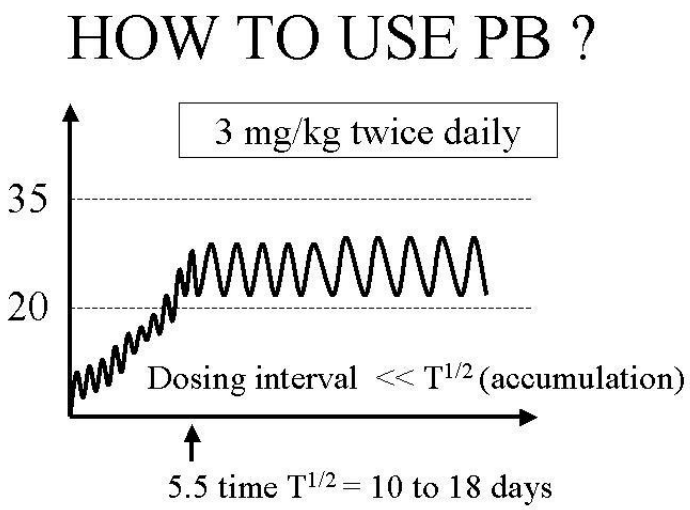
Metabolism

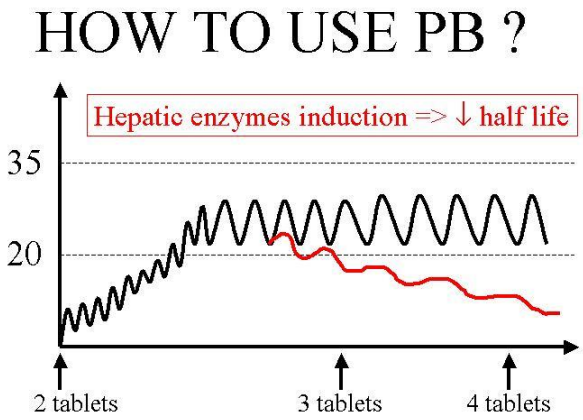
In dogs, repeated Phenobarbitone administrations are known to alter estimated steady state serum concentration as a consequence of enzyme induction (cytochrome P450 induction). This results in the need to progressively increase oral dosage with time in order to maintain steady state therapeutic level. This phenomenon of enzyme induction following repeat administration of Phenobarbitone is negligible in cats.

Pharmacokinetics

The initial elimination half-life of phenobarbitone in dogs after oral administration varies from 47 to 74 hours (dependent on genetic differences in hepatic cytochrome P450 content and the degree of prior cytochrome P450 induction). This elimination half-life is likely to significantly decrease with time following long-term phenobarbitone therapy in dogs. The elimination half-life is stable in cats at around 34 to 43 hours and therefore drug concentration of phenobarbitone are not expected to decrease in cats receiving long-term phenobarbitone therapy (due to a lack of hepatic enzymes induction following repeat oral administration of Phenobarbitone).

When a drug is introduced at a constant daily dose, serum concentrations are initially low, the amount eliminated per day is smaller than the daily dose, and drug concentration progressively increases. The amount eliminated per day increases as dose the serum concentration until it equals the daily maintenance dose. The final concentration is the steady state concentration. The maintenance dose is the daily dose necessary to maintain steady-state concentrations. The time to reach steady state is approximately five times the elimination half-life, which is 10 to 15 days in dogs and 10 to 12 days in cats.





Therapeutic Levels

The therapeutic and toxic effects of phenobarbitone are related to the serum concentration and not the quantity of drug administered orally. Monitoring of serum levels is therefore useful to assess whether therapeutic blood levels have been reached without inducing toxic effects.

The therapeutic range is 15 to 45mg/l (preferably 30 to 45mg/l in problem dogs) or 65 to 194μmol/l (preferably at least 110 to 130μmol/l in problem dogs), depending of the units used.

- If the level is below the therapeutic range it is probably having very little anticonvulsant activity and should be increased.
- If the level is above the therapeutic range then there is an increased risk of hepatotoxicity and the dose should be decreased.

Determination of serum phenobarbitone levels is indicated when:

- Steady state blood levels are reached after starting treatment (10 to 15 days in dogs and 10 to 12 days in cats). This provides a baseline to guide further changes in doses according to clinical circumstances.
- When the seizure frequency increases or the patient becomes refractory to the phenobarbitone therapy.
- Every 3 to 6 months to verify that blood concentration do not drift out of the intended range.
- When drug-related side effects are suspected

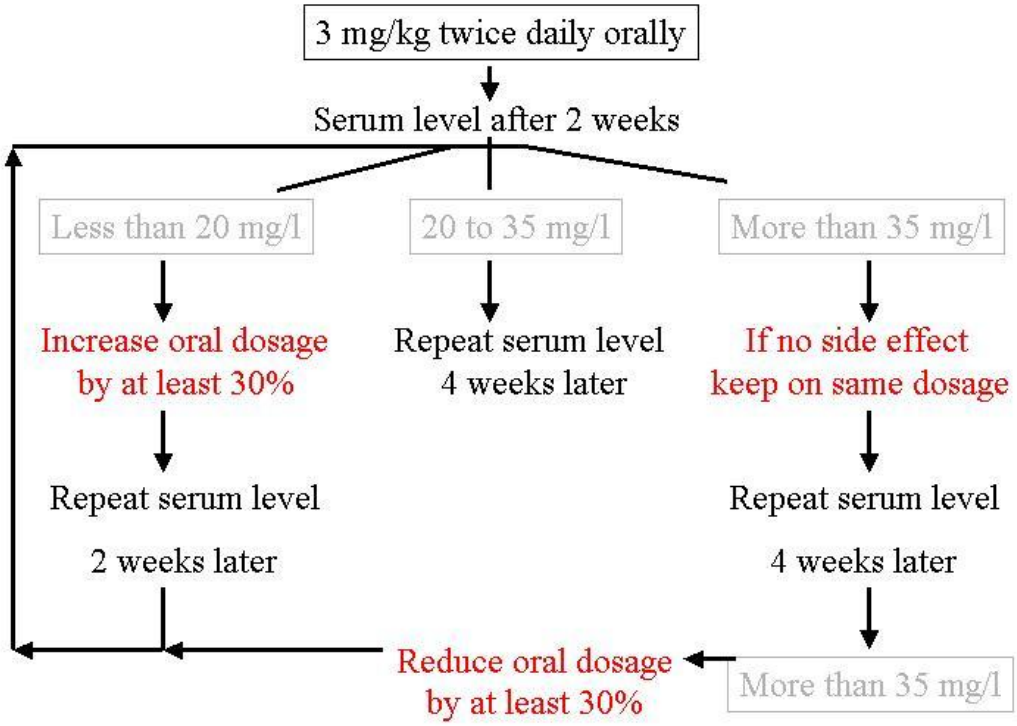
To determine the phenobarbitone blood levels:

- The half-life of phenobarbitone in dogs is 47 to 74 hours; therefore it takes 10 to 15 days for the serum concentrations to reach a steady state. After the dog has been on the **same** dose for at least 2 weeks the blood levels can be determined.

- Although blood level fluctuations may not be dramatic throughout the day in dogs with steady-state concentrations, blood samples are best taken in the early morning, prior to dosing, in a fasted dog, to maintain consistency in comparison interpretation and remove diurnal or dietary-induced fluctuations of absorption. In practice, taking the blood sample within two hours of the next dose is adequate.
- A 5ml Heparin or serum sample, spun down, and separated prior to postage, can be sent to most of the commercial laboratories.

After every change in dose the blood levels should be determined. In some cases total daily doses of up to 20mg/kg may be required to obtain therapeutic blood levels.

It may not be feasible to determine the serum phenobarbitone concentrations in every case. Where financial and owner compliance factors are not ideal, it may be justified not to determine the dog's serum levels, if the seizure frequency improves significantly on the therapy, and the dog is on a relatively low dose (i.e. there is little chance of hepatic damage).



Side Effects:

Common side effects include:

- The dog may appear sedated and ataxic (owners report the dog appears "drunk") after initiating treatment, or after an increase in the dose. This usually transient and resolves after 7 to 10 days, there is usually no need to stop the treatment.
- There may be an increase in the dogs thirst and appetite.
- Hepatic toxicity is rare, but may occur at high serum concentrations. Phenobarbitone will induce hepatic enzymes, and therefore liver function should be assessed by other parameters (AST, bile acids, albumin and urea levels). The mechanism underlying the hepatotoxicity is

unclear: it is likely to be a dose- and duration-dependent toxicity rather than an idiosyncratic hypersensitivity reaction.

Other side effects that may be evident include:

- Behavioural changes such as hyperexcitability, restlessness or sedation may occur after starting the treatment, but they appear not to be dose-related and resolve typically within 1 week.
- A more serious idiosyncratic reaction is development of an immune-mediated neutropaenia, anemia and thrombocytopaenia (most likely an idiosyncratic reaction rather than a dose-related effect). Typically, this reversible blood dyscrasia will occur within the first 6 months of dosing
- Development of a superficial necrolytic dermatitis in dogs

Mechanism of Phenobarbitone-induced Hepatotoxicity:

It is still unclear whether phenobarbitone-induced hepatotoxicity represents an idiosyncratic reaction in rare cases or is the extreme end of a spectrum of hepatic toxicosis that develops in all dogs on chronic phenobarbitone therapy.

Long-term administration of Phenobarbitone is associated with:

- Moderate increased in liver size on abdominal radiographs.
- No change in liver echogenicity or architecture on ultrasound.
- No evidence of morphologic liver damage on histology.
- Significant increased in ALP and ALT activity (“leakage” enzymes) as a result of enzymes induction rather than hepatic injury.
- Transiently decreased albumin and increased GGT.
- No changes in AST, bilirubin or fasting bile acids.

As they are not affected by the enzyme-induction effects of phenobarbitone, serum AST, bile acids, bilirubin and ultrasonographic examination of the liver are therefore useful to assess liver disease associated with phenobarbitone toxicity. In severe cases decreased albumin and urea may also be evident, although transient decreases in albumin may occur in the absence of over hepatotoxicity.

Effects of Chronic Phenobarbitone Therapy on Endocrine Function:

Phenobarbitone treatment does not affect adrenal function tests (ACTH stimulation test and low dose dexamethasone test) despite acceleration of dexamethasone metabolism.

Phenobarbitone treatment significantly decreases total-T4 and free-T4 minor fluctuation and cholesterol levels tend to increase towards the upper limits of the normal range.

IMEPITOIN (PEXION)

Mechanism of action

Imepitoin has a chemical structure similar yet distinct to the benzodiazepines. It is an imidazoline shown to have anticonvulsant effects with its main mode of action thought to be due to its properties as a low-affinity partial agonist for the benzodiazepine (BZD) binding site of the GABA receptor. Imepitoin also has a minor action of blocking calcium channels which may contribute to its antiepileptic properties. Imepitoin results in a less positively charged neuron which reduces the likelihood of an action potential developing. If a neuron cannot become excited then it cannot pass on any excitatory signals to neighbouring neurons. These mechanisms contribute to prevent the spread of electrical activity within the brain, thereby reducing the potential for seizures. Imepitoin is described as having a targeted effect. This means that it will only bind to the BZD-binding site when the neurotransmitter GABA is present. In selectively binding only when GABA is present, imepitoin works to inhibit only those neurons that are firing. In essence it potentiates the action of GABA in neurons where GABA is struggling to provide enough inhibition. It therefore only exerts its effect in overactive neurons that are stimulated during a seizure. Historically, drugs acting at the BZD-binding site have the potential for tolerance dependence and abuse liability; one such example would be diazepam. Imepitoin is known to be a partial agonist which is suggested to be an advantage over full agonists in respect of tolerance and abuse. This is because it binds less strongly for a shorter period of time. Diazepam has a high affinity for this receptor and hence serial administration can lead to a decreased efficacy over time, i.e. tolerance. Unlike diazepam, there is no evidence for the development of tolerance to imepitoin. This also gives the added advantage that imepitoin is not a controlled medication and hence can be stored safely in a veterinary dispensary without being locked away.

Metabolism

Imepitoin is metabolised via oxidative metabolism in the liver. Here, it is broken down into four main inactive metabolites which are predominately excreted in the faeces rather than in the urine. The significance of this is that no major change in pharmacokinetics or accumulation of the drug is expected in dogs with concurrent renal disease. However, due to the lack of data about the use of imepitoin in dogs with severe concomitant disease, the use of Imepitoin in dogs with severe renal disorders is contraindicated. The cytochrome P450 system is not involved in imepitoin metabolism and therefore it does not induce liver enzymes with long-term administration of the drug. This means that imepitoin has a predictable metabolism without autoinduction and hence serial blood concentration monitoring is not necessary.

Recommended dosage

The licensed dose of imepitoin is 10-30 mg/kg q12h. It is advised that dogs with newly diagnosed idiopathic epilepsy are started at the low end of this dose range and monitored. The bioavailability of imepitoin is 92% when given on an empty stomach. This reduces slightly if imepitoin is given with food and therefore, the timing of imepitoin administration in relation to feeding should be kept consistent from day to day. If the seizures remain uncontrolled then this dose can be increased by 10mg/kg q12h each

week until a maximum dose of 30mg/kg q12h is achieved. However, each dog should be assessed on an individual basis. For example, a dog with a pre-treatment seizure frequency of 1 seizure per month would require a longer observational period at the lower dose range than just one week before a decision on whether to increase the dose is required. Conversely, a dog with a pre-treatment seizure frequency of two or more seizures per week may only require an observational period of 7 days at the 10 mg/kg q12h dose before determining whether this has effectively controlled the seizure. Imepitoin has a half life of approximately 1.5 hours (although this is dose-dependent and can vary at higher and lower doses) and rapidly crosses the blood brain barrier less than 3 hours (Reference: EPAR). Therefore steady state is achieved rapidly within 3 days (Reference: EPAR) of starting or adjusting the dose of medication. It has also been shown that imepitoin does not accumulate in the plasma with repeated administration once steady state has been achieved. The short half-life also means that imepitoin is rapidly eliminated if discontinued and the dose does not need to be tapered slowly with time.

Drug monitoring

Unlike other licensed medications for canine idiopathic epilepsy, there is no requirement for repeated blood tests to monitor therapeutic serum drug concentrations or liver enzymes. Of course, biochemical screening will form an important part of initial investigations and on-going monitoring of general health is considered good clinical practice for a dog receiving chronic therapy.

Side effects

During clinical trials the adverse effects observed for imepitoin were mild and generally transient. The most commonly reported adverse effect was polyphagia, which was transient for most dogs and considered rare (between 1 and 10 dogs in 10,000). Other side effects which may be less commonly observed include hyperactivity, polyuria, polydipsia and somnolence (for full details of potential adverse effects see the Pexion SPC). Despite the potential safety benefit, the possibility of adverse effects cannot be completely excluded as is the case with all new medications entering the market.

MANAGEMENT OF REFRACTORY EPILEPSY

An animal is defined as refractory to anticonvulsive therapy when their quality of life is compromised by frequent and/or severe seizures despite appropriate therapy (usually phenobarbitone) and with serum levels within the therapeutic range. The incidence of refractory epilepsy is unknown in dogs but may be as high as 25% of patients with epileptic seizures. In the past, many of the anti-epileptics useful in humans could not be prescribed for small animals, due either to inappropriate pharmacokinetics or to potential hepatotoxicity. The result was that until recently most commonly used anti-epileptics in veterinary medicine were using the same mechanism of action, that of enhancing inhibition of the brain. Newer anti-epileptics with alternative mechanisms of action are now available, allowing a broader selection of treatment options.

However, prior to making a diagnosis of refractory epilepsy other potential causes for treatment failure should first be considered:

- Poor owner compliance (dosages missed)
- Dosage too low (determine serum concentration of phenobarbitone)
- Incorrect diagnosis (repeat investigation)
- Interference with absorption (malabsorption)
- Drug interaction affecting phenobarbitone metabolism
- Another new disease causing seizures

Poor owner compliance can be difficult to prove, but if you are strongly suspicious that the reason for the poor blood levels, despite high oral doses of phenobarbitone consideration should be given to hospitalising the animal to ensure they receive all the doses and then repeating the blood level determination. If the low blood levels were due to poor owner compliance then increased blood levels should already be evident after only a few days.

The first choice drug for use in refractory epilepsy is potassium bromide, used in conjunction with the phenobarbitone. In dogs that have severe clusters of seizures (more than one epileptic seizure in 24-hours) then there is the additional option of tactically using an additional drug during the cluster – this is in addition to the normal maintenance therapy. The drug is started after the first seizure of a cluster and continued for the normal duration of the cluster after which it is discontinued until the next cluster. This tactical use of anticonvulsants is suited to those drugs where the elimination half life is too short to warrant their use as a long-term maintenance anticonvulsant therapy and examples include: rectal diazepam formulations and long-acting benzodiazepams (Clorazepate).

POTASSIUM BROMIDE

Potassium bromide may be used in addition to phenobarbitone to help in the control of seizures refractory to phenobarbitone therapy. Potassium bromide is only introduced once the serum phenobarbitone levels reach levels of approximately 110 to 120 μmol/l (30 to 45mg/l) and the seizures are still refractory to therapy. Approximately 50% of dogs resistant to therapy with phenobarbitone alone show good control of seizures using this combination.

Potassium bromide can be used:

- As the sole anticonvulsant in dogs where phenobarbitone is contraindicated.
- In addition to phenobarbitone to help in the control of seizures refractory to phenobarbitone therapy on its own.

<u>Obtaining potassium bromide:</u>

Potassium bromide is simply and reliably obtained commercially as a suspension (Vetoquinol), tablet (Genitrix) or as a capsule (Epilease from VetPlus). The suspension is advantageous as it allows more accurate doses and simplifies dose changes. Alternatively you can make up your own solution: potassium bromide can be bought as a reagent grade chemical (request the BP grade chemical). The

powder can then be given as an oral suspension, a solution or powder packed into gelatin capsules. If you are making up your own potassium bromide then it is easiest to make up a solution with 125g of potassium bromide crystals made up to 500ml with either distilled water or syrup BP (or you can ask a local pharmacy to make up the solution). The solution should then hopefully reach a concentration of 250mg/ml.

Dose of potassium bromide:

The dosage of potassium bromide is 20 to 40mg/kg/day given once daily or divided into two daily doses. In routine cases it is advisable to start at a daily total dose of approximately 20mg/kg once daily (choose a dose based on a convenient volume of the suspension, as the dose range is quite wide). The solution is best mixed in the food.

Loading dose of potassium bromide:

In some cases the dog may need to be started on a loading dose to rapidly get the blood levels up to therapeutic levels (due to the long half-life it normally takes 3 months). The loading dose is 150 mg/kg daily for 5 consecutive days, after which the dose is decreased to the maintenance dose of 30mg/kg daily.

Monitoring KBr blood levels:

If there is poor control of the seizures, or the dog develops side effects you may want to consider monitoring the blood levels. Potassium bromide takes about four months to reach a steady serum state, after which serum levels can be determined. The serum potassium bromide concentration measured just prior to the next dosage should reach 1.0 to 2.0mg/ml to be therapeutic. It is usually advisable to determine the serum levels at about two months in problem dogs, which will give you a rough idea if the dose is too low.

Reduction of phenobarbitone dose:

In dogs on combination therapy and where there is concern regarding hepatotoxicity due to the high phenobarbitone dose, then once the dog has been on the potassium bromide for about 5 months and is showing good control of the seizures the phenobarbitone dose can slowly be tapered down, by about 7.5mg per month in a large breed dog. The dogs still need to remain on the phenobarbitone, but by reducing the phenobarbitone dose slightly, there is a greatly reduced risk of hepatic damage.

Side effects of KBr:

Side effects do not appear to be common, but can include sedation, vomiting or diarrhoea and are usually seen at the start of therapy. Another reported side effect is of pancreatitis, in dogs at risk of this problem. In addition we have had a few dogs develop hind limb ataxia (similar to CDRM in the GSD), but this usually resolves if the dose is halved or even stopped for a week. In the event of side effects developing, treatment is stopped for 2 days and then restarted at a lower level.

GABAPENTIN (Neurontin®)

The mechanism of action of the Gabapentin is unknown. Some new evidences suggest that gabapentin may facilitate the extracellular transport of GABA out of cells to act on the $GABA_A$ receptor. The dog is the only known species to partially biotransform the drug to N-methylgabapentin. A major benefit of the drug is that the parent and metabolite drugs are renally excreted; thus it will not induce drug-drug interactions with other anti-epileptic drug with hepatic metabolism (e.g. phenobarbitone). Despite its short elimination half-life in the dog which would normally exclude this drug as a maintenance anticonvulsant therapy, it may be of benefit to reduce the number of seizures in a cluster in those dogs with severe cluster seizures. The pharmacodynamic effect is believed to outlive the known half-life of the drug. Recommended dosages in dogs are 30 to 60 mg/kg/day divided two to three times daily. Serum monitoring is not recommended as the drug as a very high therapeutic index and little drug-drug interaction. Gabapentin is particularly useful in epileptic dogs with underlying hepatic disease. One of the main limitations to the use of this drug is its cost. When used in combination with phenobarbitone and bromide in dogs with refractory idiopathic epilepsy, the number of seizures per week and the number of days with any seizures in a one-week period were significantly reduced in 6 out of 11 dogs in our study (Platt, Adams, Garosi 2006, Vet Record).

LEVETIRACETAM

This drug appears to have a different mechanism of action when compared to existing antiepileptics, which may prove advantageous in polytherapy. It has rapid and complete absorption after oral administration with minimal excretion in the bile, no significant protein binding, lack of hepatic metabolism and linear pharmacokinetics. Over 80% of the drug is eliminated in the urine in dogs. The lack of hepatic metabolism is beneficial when it is used with other drugs that are primarily metabolized by the liver such as phenobarbitone. The half-life in dogs is 4 to 6 hours, which would necessitate frequent administration. As for gabapentin, the pharmacodynamic effect is believed to outlive the known half-life of the drug. The recommended dose is 60 mg/kg/day divided every 8 hours. It is the best tolerated of all new antiepileptics in human clinical trial.

ZONISAMIDE

Zonisamide is a substituted 1,2-benzisoxazole derivative that works by both blocking the propagation of epileptic discharges and suppressing focal epileptogenic activity. It is well absorbed and has a relatively long half-life and high protein-binding affinity. Zonisamide is hepatically metabolized and thus is influenced by concurrent administration of other similarly metabolized drugs. It can be an efficacious and well tolerated drug in the dog with recurrent generalized epileptic seizures refractory to phenobarbitone and/or potassium bromide therapy. Initial dose is 5 – 10 mg/kg/day. Major possible adverse effects include sedation, ataxia and loss of appetite.

TOPIRAMATE

Topiramate blocks seizure spread by rapidly potentiated GABA activity in the brain. Its pharmacokinetic has not been studied to this date in dogs. In human, twice-daily dosing is recommended due to its relatively long half-life of 20 to 30 hours. Recommended dosages in dogs range from 2 to 10 mg/kg twice daily.

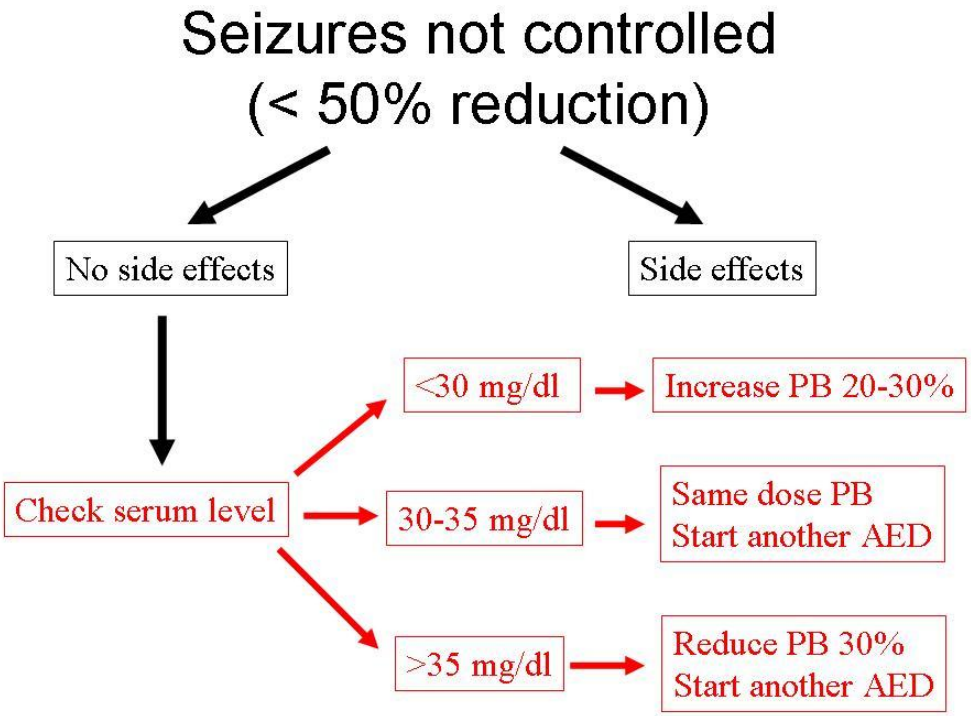
RECTAL DIAZEPAM

Tactical use of rectal diazepam in dogs with severe cluster seizures has been shown to be of benefit to reduce the total number of seizure events during a cluster. Rectal absorption is comparatively more rapid than i/m or p/o absorption (within 10 minutes) and potentially avoids some of the first pass effect observed after p/o administration as a portion of the venous return from the rectum bypasses the portal circulation. The recommended dose is 0.5 to 2 mg/kg for a maximum of three treatments within 24-hours. The use of this drug formulation should be subject to owner selection as there is the potential for injury to the dog and over-dosage.

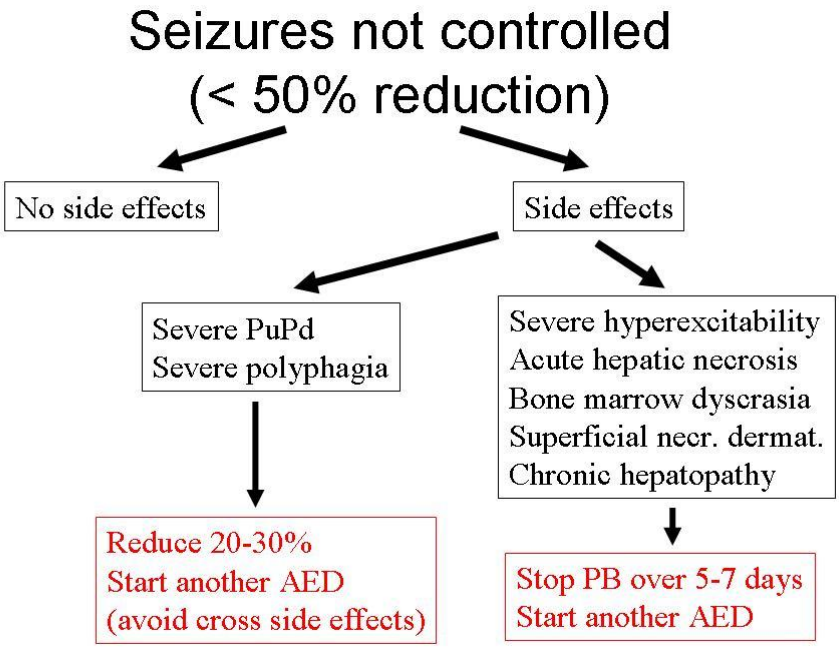
RATIONAL CHOICE OF ADDITIONAL ANTI-EPILEPTIC DRUG (AED) IN REFRACTORY EPILEPSY

An animal is defined as refractory to antiepileptic therapy when its quality of life is compromised by frequent and/or severe seizures despite appropriate therapy (usually phenobarbitone) and/or side effects of medication. Side effects of phenobarbitone in dogs can be idiosyncratic (severe hyperexcitability, acute hepatic necrosis, bone marrow dyscrasia, superficial necrolytic dermatitis, dyskinesia) or dose related (polyuria, polyphagia, ataxia, sedation). Serious liver toxicity is less common and may be more likely with serum level maintained above 35 mg/l. Side effects in cats are minimal and include mostly sedation and ataxia. Occasionally, cats treated with phenobarbitone have been reported with clinico-pathologic abnormalities including leucopenia and thrombocytopenia, as well as immune-mediated hypersensitivity reactions (severe cutaneous eruptions and marked lymphadenopathy), all of which are reversible with discontinuation of the drug. Decision on altering (or discontinuing) phenobarbitone and adding another anti-epileptic drug is based on seizures controlled (at least 50% reduction in seizures' frequency) and presence, but also type, of side effects:

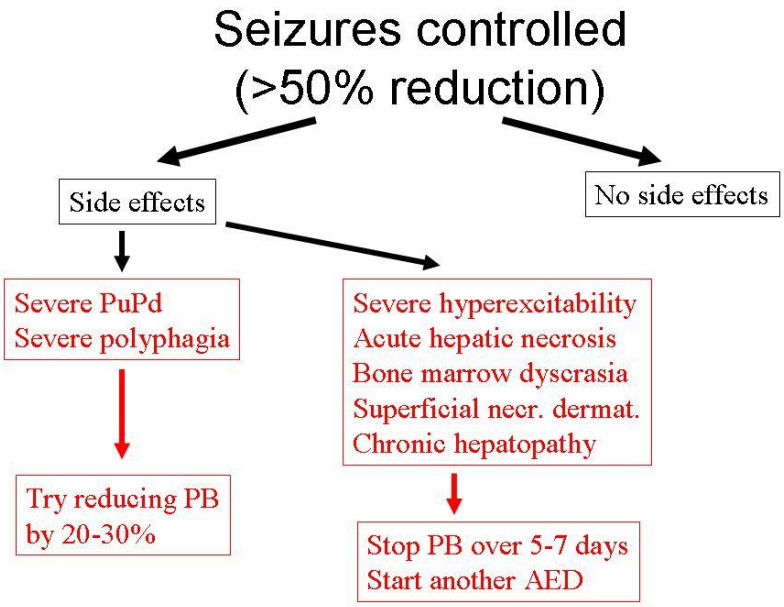
Seizures not controlled but no side effects: Serum phenobarbitone should be checked. If serum level is > 35 mg/dl, another AED should be started, oral phenobarbitone dosage should be slowly reduced (aiming to reach serum level below 35 mg/dl) to limit risk of liver toxicity. If serum level is in the high end of therapeutic range (30 – 35 mg/dl), another AED should be started while keeping the animal (at least initially) on same dosage of phenobarbitone. Bromide loading (6 per rectal boluses of 100 mg/kg q4h or 150 mg/kg/day orally over 5 consecutive days) or use of AED with rapid onset of action (levetiracetam, zonisamide, pregabalin) may be required in case of high seizures' frequency. If serum level is < 30 mg/dl, oral dosage should be increased targeting to reach serum level in the high end of the therapeutic range.

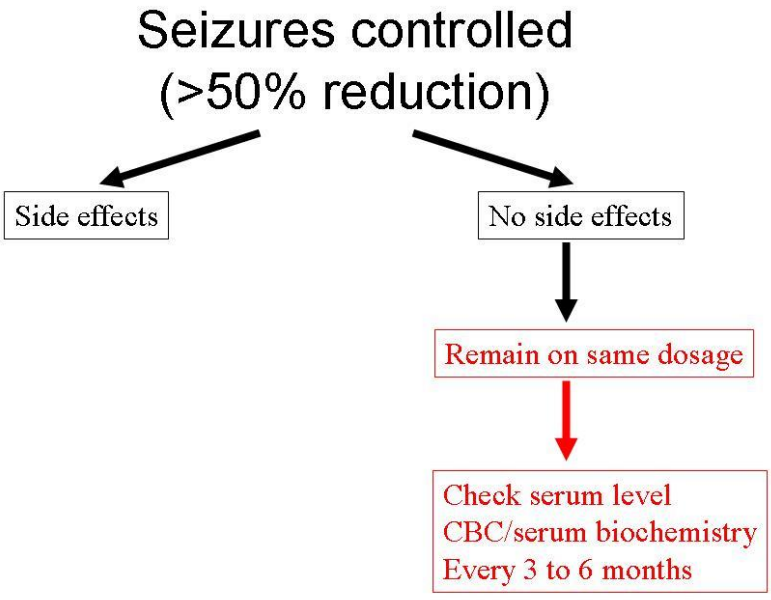


Seizures not controlled and side effects: In case of idiosyncratic side-effects, the animal should be started on another AED (ideally bromide loading or AED with rapid onset of action) while taking the animal off phenobarbitone over 5 -7 days period. In case of severe polyuria/polyphagia/polydipsia, another AED should be started avoiding using drug with similar side effect profile (eg bromide). Attempt should be made at the same time to reduce phenobarbitone dosage to minimise these side effects.



Seizures controlled but side effects: In case of severe polyuria/polyphagia/polydipsia, attempt should be made to first reduce phenobarbitone dosage to minimize these side effects while maintaining seizures' control. If face with idiosyncratic side-effects, the animal should be started on another AED (ideally bromide loading or AED with rapid onset of action) while taking the animal off phenobarbitone over 5 -7 days.





Maintenance anti-epileptics for use in dogs (TSS = approximate time to steady state)

Antiepileptic drug (dogs)	**T ½ (hrs)**	**TSS (days)**	**Suggested serum therapeutic range**	**Recommended dose**	**Possible Side Effects**
Phenobarbitone	32-89	10-18	20-35 mg/dl	2-3 mg/kg PO q12h	Sedation; ataxia; PuPd polyphagia; hyperexcitability; hepatotoxicity; induces P450 system; bone marrow dyscrasia; pancreatitis
Imipetoin	1.5	2	N/A	10-30 mg/kg q12h PO	Polyphagia PuPd; hyperactivity; somnolence
Potassium Bromide	21-24 days	2.5-3.0 months	1-3 mg/ml	20-40 mg/kg/day PO	Sedation; weakness; polydipsia-poyuria; polyphagia; pancreatitis; pruritis; behavioural changes
Felbamate	5-6	1-2	25-100 mg/L	15-70 mg/kg q8h PO	Blood dyscrasias; liver disease; dry eye
Topiramate	20-30	3-5	2-25 mg/L	2-10 mg/kg q12h PO	Vomiting; diarrhoea; sedation
Clorazepate	5-6	1-2	20-70µg/L (nordiazepam)	0.5-1.0 mg/kg q8-12h PO	Sedation
Zonisamide	15-20	3-4	10-40 µg/mL	2.5-10.0 mg/kg q12h PO	Sedation; loss of appetite; dry eye; ataxia
Gabapentin	3-4	1	4-16mg/L	10-20 mg/kg q8h PO	Sedation; ataxia
Levetiracetam	3-4	1	Not known	10-20 mg/kg q8h PO	Sedation; ataxia
Pregabalin	7	2-3	>2.8µg/mL	3-4 mg/kg q8h-q12h PO	Sedation; ataxia