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Medical Neurology for Advanced Practitioners Mini Series

Session Two: Seizures - A Case Based Approach to Help with the Frustrations

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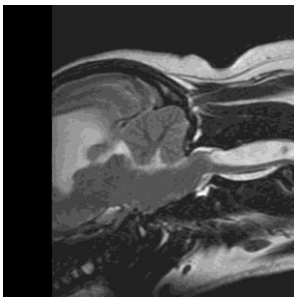


Seizures and Paroxysmal Movement Disorders

Introduction

Seizures and epilepsy are the most common neurological disorder seen by veterinary practitioners - more common than ataxia, more common than head tilts and circling. They represent up to 5% of all presentations to vets, and therefore are something we all need to be comfortable dealing with. The good news is that unlike the last module, there's not much neuroanatomy to remember since seizures can only be generated by one part of the nervous system: the forebrain.

Tremors and movement disorders, on the other hand, can arise from a couple of different places, and we'll go through these slightly separately. But by the end of this we hope to have got you up to speed with the latest on seizure and tremor disorders, and maybe even introduced you to some of the exciting new developments in the frontiers of epilepsy research.

Objectives of the Module:

By the end of this module, all going well, you should be pretty relaxed about the following:

- **Seizure classification:** what is a seizure, what types of seizure exist (and how do we classify them?), what do different seizure types indicate?
- **Seizure pathophysiology:** what are the basic mechanisms that underlie the development of seizures? (and what causes seizures to terminate?)
- **Investigation of seizure disorders:** what are the differential diagnoses for a patient presenting with seizures? How do we go about making a diagnosis?
- **Seizure management:** What anticonvulsants are available for treating seizures in dogs and cats? When would you choose one over the other and what are the advantages and disadvantages of each? What sort of success do we expect when treating seizures?
- **Status epilepticus:** how do you manage a patient with a seizure that does not terminate of its own accord?
- **Tremors:** what are the differential diagnoses for patients presenting with tremor disorders? How are they treated?
- **Paroxysmal movement disorders:** what are they and what are the proposed underlying mechanisms?

Introduction to epileptic seizures and other paroxysmal disorders

Before we start we need to have a few words on terminology.

There is significant variability and overlap in the clinical presentation for seizures and other types of movement disorders. This makes life tricky for the practitioner who has to recognize and understand the etiology and treatment of these disorders - in particular, misdiagnosis may lead to inappropriate or ineffective treatments or side effects of those treatments. In addition communicating with other practitioners is made more difficult by the vague and imprecise use of words like 'fit' and other synonyms for seizures. For this reason, it's worth a five minute review of some definitions:

Seizure

Literally, the term seizure refers to 'a sudden attack, spasm or convulsion, as occurs in epilepsy'. This usually implies a transient event, that may be a dramatic or catastrophic event. Going by this dictionary definition, the term is non-specific and is often used interchangeably with convulsion. As neurologists we usually use the term 'seizure' to signify transient, unregulated, excessive depolarization within a group of neurons within the brain. This last bit is important for a couple of reasons - firstly, we think of a seizure as an electrical event. When those neurons within the brain that control motor function are depolarizing excessively, motor manifestations of the seizure occur, but this is not 100% of the time. Secondly, this implies that manifestations of seizure activity can occur in other ways, such as a loss of consciousness, visual or auditory manifestations etc.

Epileptic seizure

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

Epilepsy

Epilepsy is not a specific disease but a condition characterised by recurrent 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 described 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 but a clinical sign indicative of a forebrain disorder - a bit like a cough is a sign of airway disease rather than the disease itself. 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.

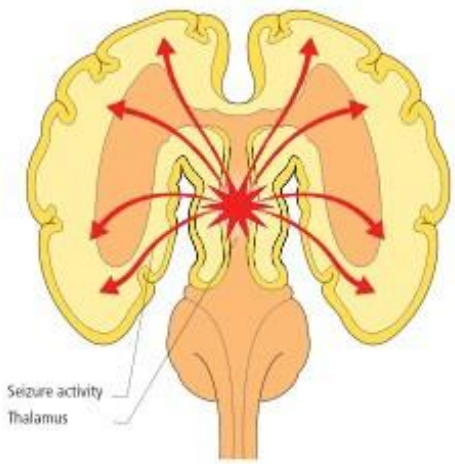
Classification of epileptic seizures

Now that we are clear about terminology, how do we classify epileptic seizures and how this could be helpful in your diagnostic approach?

Seizures can be classified into two major categories: partial and generalized.

Generalised seizures

A generalized seizure describes one in which there is no apparent seizure focus - the seizure phenomenology suggests that all parts of the forebrain are affected from the onset rather than one region being the origin of seizure activity which then spreads to other areas.



Generalised seizure activity results from a synchronized electrical discharge from the whole of the forebrain (From Platt S & Garosi L. Small Animal Neurological Emergencies. Manson publishing, 2012).

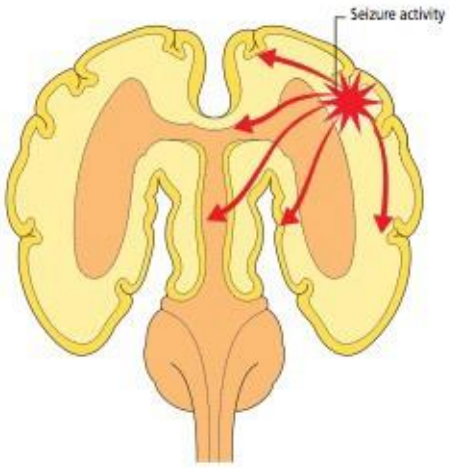
In dogs the most common form, generalised tonic-clonic seizures (i.e., "grand mal") are the most common type of all seizures. Consciousness is impaired and motor manifestations are bilateral throughout the body. The tonic phase typically lasts about 10-30 seconds in which limbs and neck muscles are stiff, 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

Absence seizures (referred to as "petit mal" in people) 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. In people they represent the most common type of childhood seizure and are often accompanied by a 3Hz twitching of the eyelid or side of the mouth. They may occur at a rate of many hundreds per day and commonly go undiagnosed as they do not progress to other seizures and may significantly impair social and intellectual development.

Partial seizures

A partial, or focal seizure, occurs when the seizure focus is present in one area of the cerebral hemispheres, and the abnormal neuronal depolarisation remains restricted to that region.



Partial seizure activity results from an abnormal electrical discharge in a single area of the brain. The area from which the focus originates determines the clinical characteristics of the focal seizure (From Platt S & Garosi L. Small Animal Neurological Emergencies. Manson publishing, 2012)

As a result the clinical signs reflect the fact that only a single area of the brain is affected. Any portion of the body can be involved during a focal seizure depending on the location of the seizure focus. The focal nature of this seizure type is associated with a higher incidence of focal intracranial pathology (presence of a structural lesion) in cats, as compared with dogs (overall cats suffer from focal seizures more commonly than dogs). The various forms of partial seizure include:

Simple Focal (partial motor) seizures

Unaltered consciousness with asymmetric localised motor signs such as eyelid or facial twitching, clonus of muscle groups of one limb (don't forget that the side of the body affected is the contralateral side to the seizure focus).

Complex partial seizures

These seizures show similar motor signs to simple partial seizures, but consciousness is impaired in these patients.

Psychomotor seizures: Psychomotor seizures are typically considered a subtype of complex partial seizures. They manifest as behavioural seizures pattern which may present as rage, aggression without provocation, fly-catching, running in circles, floor licking, vocalization, tail chasing, etc. The behavioural abnormalities seen in psychomotor seizures have been suggested to imply involvement of the limbic system.

Partial seizures with secondary generalization

A seizure may start restricted to a focal region of the brain only to spread throughout both cerebral hemispheres, resulting in a focal seizure with secondary generalization. Some patients presenting for generalized tonic-clonic seizures, after close questioning of the owner, can be shown to have an initial partial seizure that then progresses in this way.

How to tell if it is an epileptic seizure?

The recognition of an epileptic seizure is essentially based on the owner's description of the event. A typical seizure consists of 3 phases: a pre-ictal phase (also known as the aura), the ictus itself, and a post-ictal phase.

The **pre-ictal phase** consists of behavioural changes - animals often become clingy or anxious and follow their owners closely. This may continue for up to 20 or 30 minutes or may not occur at all in some patients.

The **ictus** itself depends on the nature of the seizure - with generalized tonic-clonic seizures this is usually easily recognized, with loss of consciousness, tonic and clonic phases easily recognizable.

During the **post-ictal phase**, brain function has not returned to normal although seizure activity has finished. Patients commonly display abnormal behaviour patterns or changes in vision. They may appear blind, confused, aggressive, and commonly run with no obvious cause.

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, diagnostic and treatment approaches of movement disorders

Introduction

The term dyskinesia specifically means "difficulty performing a voluntary movement". Often this is due to other involuntary movements of the body that prohibit the voluntary movement. Technically speaking, then, a paroxysmal (i.e., episodic) dyskinesia is a broad general term that could include nearly any seizure or movement disorder. The most common presentation is dystonia (involuntary sustained contraction of a group of muscles producing abnormal posture) of the limbs. Loss of consciousness and awareness is not a feature which may help differentiate from some epileptic seizure activities.

There are several classification schemes for episodic dyskinesias based on duration, onset, and the presence/absence of specific triggers for the episode. The following classification has been established in human neurology:

- **PKC/PKD**: Paroxysmal kinesigenic choreoathetosis/dyskinesias - brief (seconds to 5 mins) frequent (up to 100/day) dyskinetic attacks provoked by sudden movement. Attacks are usually unilateral and consciousness is never lost. Can be idiopathic, familial, or secondary. Ion channel disorder suspected, but true pathophysiology not confirmed; could be subcortical (basal nuclei) also. Anti-epileptic drugs (particularly carbamazepine) are helpful in many cases in man. Acetazolamide may also help (potassium channel disorder?).

- **PDC/PKND**: Paroxysmal dystonic choreoathetosis/Paroxysmal non-kinesigenic dyskinesias - Long duration attackes of 10 mins to 4 hrs; can go months without attacks. Attacks are long-duration, induced by a variety of factors but not sudden movement. Can be idiopathic or symptomatic. Anti-epileptic drug are generally not effective. Clonazepam may help however to drug is particularly effective in man, best to just avoid precipitating factors.

- **PED**: Paroxysmal exertion-induced dystonia - Rare; perhaps thought to be intermediate form of PDC but without association with precipitating factors. Attacks last 5 to 30 mins, and consist mainly of dystonia induced by prolonged exercise. Anti-epileptic drug are generally unhelpful.

- **Episodic ataxias** - Attacks consist of acute onset cerebellar ataxia lasting from seconds to minutes (EA-1), or minutes to days (EA-2). EA-1 attacks are triggered by startle, exercise, sudden movement, and stress; and are associated with persistent interictal facial myokymia, or rarely, with PKD. Nystagmus is not present with EA-1. EA-2 attacks are triggered by physical or emotional stress, alcohol, carbohydrate, or coffee; and are associated with interictal nystagmus. Occasionally vertigo, nausea, visual abnormality, confusion... Acetazolamide is the drug of choice in human. Anti-epileptic drug may help in some cases.

Paroxysmal movement disorders have been described in a number of breeds (Cavalier King Charles spaniel, Border Terrier, Cairn Terrier, Scottish Terrier, Dalmatian and Norwich Terrier, Boxer, Bichon Frise, Chinook) where they have been 'labelled' as breed specific entities (Scottie cramp in Scottish terrier, Hypertonicity in Cavalier King Charles Spaniels, episodic dyskinesia in Chinook, Canine Epileptoid Cramping Syndrome CECS in Border terrier also known as Spike's disease). Although not reported in the literature, similar paroxysmal movement disorders can be seen in other breeds and especially young Labrador retrievers, Wheaten terriers, Springer Spaniels, Dalmatians, and miniature poodles. Most paroxysmal movement disorder seen in dogs and cats would be the equivalent of Paroxysmal dystonic choreoathetosis/Paroxysmal non- kinesigenic dyskinesias.

VIDEO TOUR OF PAROXYSMAL MOVEMENT DISORDER

- Hypertonicity in CKCS
- Canine epileptoid cramping syndrome
- Labrador retriever dyskinesia
- Paroxysmal dyskinesia in other breed

(Videos Available Online)

PATHOPHYSIOLOGY

The neuroanatomical basis for this collection of involuntary muscle movements is unknown. In most instances, these conditions are rarely life threatening or incapacitating to the affected animal therefore large-scale studies with thorough histological evaluation of the nervous system of affected animals has not been performed. Where investigations have been done, a functional disorder likely involving abnormal neurotransmitters or their receptors has been speculated.
Structural lesions are usually absent.

Candidate gene analysis has recently identified a microdeletion affecting the brevican gene (BCAN) in Border terrier with so-called CECS, which encodes the brain-specific extracellular matrix proteoglycan brevican. DNA testing is now available via Laboklin.

CLINICAL PRESENTATION

In an affected animal, abnormal movements may not be stereotypic, varying not only in duration and frequency but also in affected muscle groups.

The most common clinical presentation is dystonia involving the pelvic limbs, which clinically appears as increased extensor tone of the limbs. While all four limbs may be affected, the pelvic limbs are often affected to a greater degree than the thoracic limbs.

Affected animals can also be severely incapacitated by an inability to move limbs with sustained contraction of extensor or flexor muscle groups. Episodes are often triggered by excitement or exercise. Loss of consciousness and awareness is not a feature of these conditions, which may help to differentiate from some epileptic seizure activities. Autonomic signs such as urination, salivation and defecation are not seen.

DIAGNOSIS

The most important differential diagnosis for paroxysmal movement disorders is simple, partial (focal) seizures. Such disorders are recognized in animals with stereotypic, episodic muscle movements. As such, they can be easily misconstrued as a paroxysmal movement disorder.

Given the difficulty in the clinical differentiation from simple partial (focal) seizures along with a lack of a defined diagnostic algorithm for paroxysmal movement disorder, strong consideration should be placed on pursuing diagnostic testing aimed at eliminating structural disease of the CNS from consideration. Obtaining a video footage of the event from the owner is an important part of the diagnosis to help differentiating from an epileptic seizure

Consequently, performing an MRI scan of the brain along with cerebrospinal fluid (CSF) analysis is recommended to eliminate an underlying structural brain disease.

Complete blood count, biochemical evaluation, and urinalysis to exclude underlying metabolic (including organic acidurias) or endocrine disorders should also be considered prior to evaluation of possible structural brain disease.

TREATMENT

Treatment guidelines for paroxysmal movement disorder are unclear. Anti-

epileptic medications are rarely effective.

Most CKCS with hypertonicity respond completely to the use of the carbonic anhydrase inhibitor acetazolamide (4-8 mg/kg PO q8-12hrs).

Clonazepam (0.5 mg/kg PO q8-12hrs) can be used as add-on to acetazolamide in refractory cases, but its effects may not be life-long, as functional tolerance tends to develop.

A functional deficiency in serotonin modulation of motor neuron function has been postulated in Scottie cramp. Signs can be induced with exercise 2 hours after administering methylsergide (0.3 mg/kg orally), a serotonin antagonist. Treatment is aimed at muscle relaxation or increasing serotonin levels. Although not currently documented, the use of serotonin reuptake inhibitors may be useful for treatment of this condition in Scottish terrier.

Hypoallergenic dietary therapy has been proposed with variable success in Border terrier with so- called CECS.

Other paroxysmal events which could mimic an epileptic seizure

Determination of the cause of a paroxysmal event can be particularly challenging especially considering that the animal is often presented to you in between these events. The only information you may have to work your way through a diagnosis is the description of the event provided by the owner.

> ***Non-neurological causes*** include cardiovascular, respiratory or orthopaedic disease.
>
> ***Neurological causes*** ranges from epileptic seizures, narcolepsy/cataplexy, neuromuscular disorders, paroxysmal movement disorders, metabolic causes of central and/or peripheral nervous system dysfunction, vestibular attack and myokymia.

A thorough description of the event, especially if supported by video footage, can provide important information about the speed of onset of neurological signs, potential loss of consciousness/awareness during the events and type of activity the patient was performing at the time of the 'episode'. A complete physical and neurological examination, combined with the information on the signalment and anamnesis represents the first and one of the most important steps in distinguishing if the weakness/collapse originates from a primary neurological condition (including neuromuscular or central nervous system diseases) or is caused by cardiovascular, respiratory, metabolic or orthopaedic disorders.

The table below (taken from Small Animal Neurological Emergencies by Platt SR and Garosi LS) below provide a summary of common paroxysmal disorder which could be confused for an epileptic seizures and criteria you can use to differentiate them.

Table 1 **Differentiation of non-epileptic paroxysmal events from epileptic seizures**

PAROXYSMAL EVENT	PRECIPITATING FACTORS	LEVEL OF CONSCIOUSNESS	FLACCID OR SPASTIC COLLAPSE	INVOLUNTARY MOVEMENT DURING EVENT	POSSIBLE HISTORICAL FINDINGS	POSSIBLE PHYSICAL EXAMINATION FINDINGS
Narcolepsy	Excitement/feeding	Absent	Usually accompanied by cataplexy	No	Often purebred dog with early age onset	Normal
Cataplexy	Excitement/feeding	Normal, if not accompanied by narcolepsy	Flaccid	No	As for narcolepsy	Normal
Neuromuscular collapse	Activity/exercise	Normal unless impaired by respiratory compromise	Often flaccid (e.g. myasthenia gravis). Can appear spastic in some cases of myopathy	May appear to be present when attempting to stand	May be accompanied by dysphagia, dysphonia, regurgitation	May be normal or may be muscle atrophy, muscle pain and or reduced reflexes
Syncope	Exercise, excitement, cough	Reduced to absent	Flaccid	No	May be accompanied by cough, increased respiratory noise	Arrhythmia, pulse deficits, murmur, abnormal lung auscultation, cyanosis
Movement disorder	None, to excitement/activity/ exercise	Normal	Often spastic	Yes; exacerbated by attempts to stand	May be purebred with early age onset	Normal
Metabolic collapse e.g., hypoglycaemia	May be related to feeding times/excitement	Variable; long lasting	Often flaccid. Can be spastic in some cases (e.g. hypocalcaemia)	No, except facial twitching in some cases of hypogly-caemia or hypocal-caemia	Anorexia, depression, polyuria, polydipsia, vomiting, weight loss	May be normal; weight loss
Sleep disorder	Sleep	Absent (REM sleep) and may progress to apparent wake-fulness during event	Either	Yes; REMs during event	Never occurs during periods of normal consciousness	Normal
Vestibular event	Variable	Normal to depressed	Usually spastic	Attempts to stand; nystagmus	Periods of head tilt and or ataxia; head tremor; ear disease	Normal to nystagmus, head tilt, ataxia, vomiting

Neuroanatomical basis of seizure activity

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). intracranial causes may be further subdivided into functional disorders (where no gross structural changes are evident in the brain and the cause is probably a neurochemical dysfunction) and structural disorders (where there is a gross structural cause within the brain [e.g. a brain tumour or encephalitis]. Extracranial causes include toxicities and metabolic disturbances that either interfere with CNS function or are directly neurotoxic.

On that basis, epileptic seizures are aetiologically categorised as:

- **Reactive epileptic seizures:** This term is often used to describe seizures resulting from an extra-cranial cause and include metabolic and toxic 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.
- **Idiopathic epilepsy:** This term is often used to describe recurrent seizures resulting from a functional intra-cranial cause (e.g. Idiopathic Epilepsy). The term implies a suspected genetic basis for the seizure activity for which the underlying disorder is frequently suspected to be a transient functional or neurochemical abnormality. The diagnosis of idiopathic epilepsy is unfortunately a diagnosis of exclusion as there is currently no definitive diagnostic test to confirm the diagnosis.
- **Secondary (or symptomatic) epilepsy:** This term is often used to describe recurrent seizures resulting from a structural intra-cranial cause (e.g. brain tumour). 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.

The table below summarizes the most common presentation, results of neurological examination and diagnostic test findings based on neuro-anatomical basis for the seizures.

Most Common Presentations Based on Anatomic Diagnosis

Functional (intracranial) e.g. Idiopathic Epilepsy

- Generalised seizures (rarely partial)
- Initially low frequency
- Normal neurological examination in the interictal period
- Normal CSF analysis
- Normal brain imaging

Structural Intracranial Causes

- Partial or generalised seizures
- Variable frequency
- Neurological deficits in the inter-ictal period (except lesion in 'silent' areas of the brain or in early stages of an enlarged mass)
- Normal or abnormal CSF analysis
- Usually abnormal brain imaging

Extracranial Causes

- Generalised 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

Toxins associated with seizure activity in dogs and cats

Although a large number of toxins can cause seizures in dogs and cats, they are often causing sudden onset of multi-systemic clinical signs and severe cluster seizures/status epilepticus. A toxin is therefore a very unlikely cause of recurrent seizures in the absence of other clinical signs.

Idiopathic epilepsy

Idiopathic (inherited) epilepsy has been documented in Beagles, German Shepherds, Belgian Tervurens, Keeshounds and Dachshunds and is also suspected in Saint Bernards, Australian Shepherds, Labrador Retrievers, Golden Retrievers, Irish Setters, Standard Poodles, Springer Spaniels, Cocker Spaniels, Lhaso Apsos, Border Collies and many other pure breed dogs.
Idiopathic epilepsy is also reported in cats although some authors have argued that this is much less common than other forms of epilepsy.

Generalized seizures with loss of consciousness are most common and usually begin between 1-3 years of age but a few dogs begin seizures between 6 months and 1 year or 3-7 years of age. The onset of seizures is almost always insidious, beginning with a seizure every few weeks or months but then becoming progressively more frequent. Many dogs eventually develop cluster seizures or status epilepticus and in rare cases, this may be the first known seizure activity. German Shepherds, Australian Shepherds, Belgian Tervurens, Springer Spaniels, Labrador Retrievers and Saint Bernards are prone to cluster seizures.

The diagnosis is suspected in a purebred dog with generalized seizures and normal findings on the physical and neurologic examinations between seizures and all diagnostic tests including MR imaging and CSF analysis. Breeding trials may be needed to confirm the diagnosis if no other dogs in the lineage have had seizures. Unless animals are presented with severe cluster seizures or status epilepticus, therapy is aimed at controlling the seizures with maintenance antiepileptic therapy.

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.

The treatment of idiopathic epilepsy is only symptomatic and aims to reduce the frequency and severity of seizures with minimum potential side-effects while maximizing the owner's and the dog's quality of like.

Clinical approach to suspected epileptic seizures

STEP 1: Obtain a good history

Often an owner may describe an event that gives rise to suspicion of an epileptic seizure, but the animal may be normal. It is vital that the clinician asks specific questions which will help to determine whether the event could have been an epileptic seizure and what the underlying cause may be:

- Age at the onset of the first seizure event: idiopathic epilepsy is the most likely cause on a dog having its first seizure between the age of 6 months and 6 years. The table below summarizes likely causes of seizures depending on age of onset (most likely causes are in bold).

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)
- Neosplasia

Adult (more than 6 years old)

- **NEOPLASIA**
- **Metabolic (e.g. hypoglycemia secondary to an insulinoma)**
- **Inflammatory/infectious CNS disease**
- Head trauma
- Toxic causes (e.g. organophosphates)

- Owner's description of these episodes, including pre-ictal signs, the seizure episode itself (including autonomic nervous system involvement, e.g. salivation and urination) and post- ictal signs.
- Frequency of these episodes: will help to decide about starting anti-epileptic treatment and monitoring treatment response.
- What was the animal doing just before the episode occurred:consistent signs exhibited by the animal prior to the event, such as behavioural abnormalities, are more suggestive of an epileptic seizure than other possible paroxysmal disorders such as narcolepsy or syncope.

- Relationship of episodes to exercise or feeding: seizures following feeding may be associated with hepatic dysfunction or seizures during fasting, exercise or stress may be associated with hypoglycemia.
- Behaviour, mental status, gait between episodes (inter-ictal period): If the animal is abnormal between well spaced seizure events, then seizures from extracranial disorders or symptomatic epilepsy are more likely.
- Is there any abnormality evident after the possible seizure event: identification of a post- ictal phase can be important to confirm seizures, as this activity is not seen with syncope, narcolepsy or REM sleep disorder.
- Seizure length: most epileptic seizures last a few seconds or minutes. Consideration to other paroxysmal events (especially paroxysmal movement disorder) should be given to any events lasting longer than expected for an epileptic seizure.
- Any other systemic signs.
- Previous medical history including past head injury.
- Vaccination status.
- Travel history.
- Any familial history of seizures.

STEP 2: Evaluate the animal for signs suggestive of a forebrain disorder

From a neuro-anatomical basis, an epileptic seizure refers to a forebrain dysfunction. At a minimum, the neurological examination should therefore focus on detecting forebrain signs (evaluation of mental status, presence of circling gait, postural reaction testing, assessment of menace response and response to nasal stimulation). The table below summarizes likely causes of seizures depending on the results of the inter-ictal neurological examination depending on the presence or not of neurological signs and their symmetry or lack of it.

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
- Midline structural brain disease (e.g. pituitary tumour)
- (Degenerative disease)

Abnormal inter-ictal examination and asymmetrical neurological deficits

- Structural brain disease (neoplasia, inflammatory/infectious, previous head trauma or malformation)

In the event that the neurological examination suggests a diffuse and symmetrical cerebral lesion consideration should be given to an extra-cranial cause of the seizures, e.g. a metabolic encephalopathy such as hypoglycaemia or hepatic encephalopathy.

The detection of forebrain signs on neurological evaluation in the inter-ictal period rules-out as a general rule the hypothesis of idiopathic epilepsy. However there are two exceptions to this:

- Depression of forebrain activity occurs during the period immediately following an epileptic seizure (so-called post-ictal depression). During this period subtle neurological deficits, including conscious proprioceptive deficits, may be evident. Post-ictal depression lasts a variable amount of time, but most cases return to normal a few hour (up to a day) following the seizure episode.
- Neurological deficits may also result secondary to severe or prolonged seizures due to hypoxic injury or the so-called excitotoxicity phenomenon. Such lesions are particularly evident in the grey matter in regions such as the hippocampus, piriform lobe and in severe cases in the grey matter adjacent to the hippocampus.

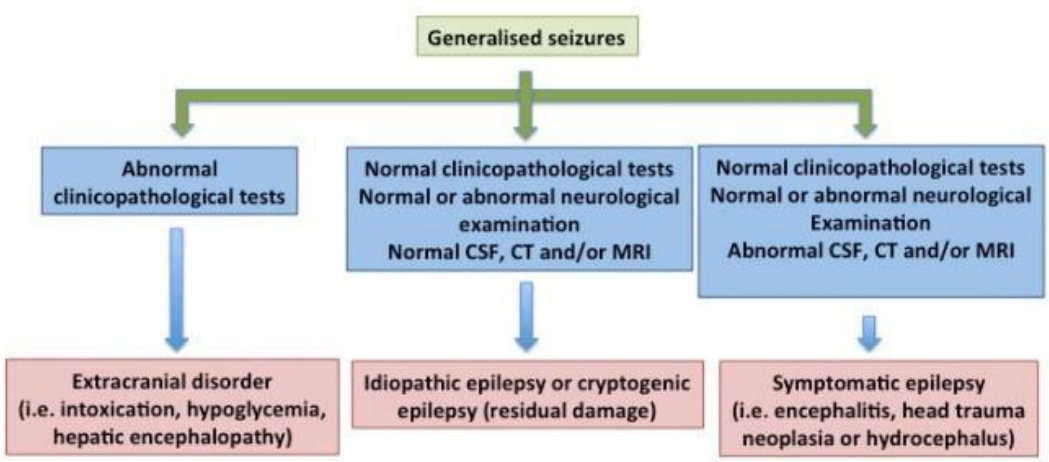
STEP 3: Specific diagnostic tests

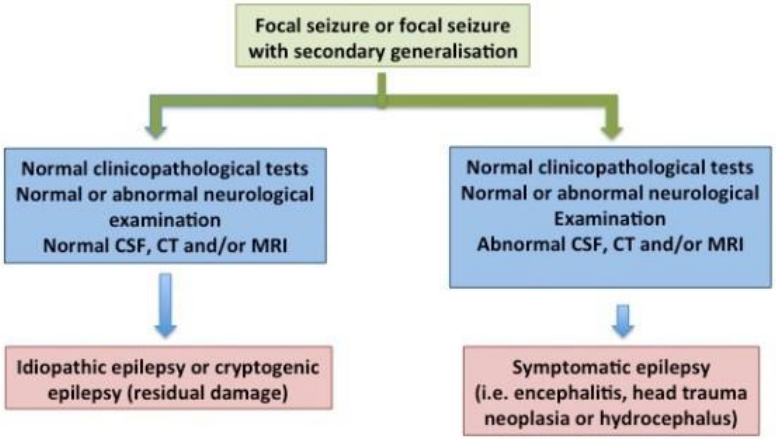
It would not be unreasonable to make a diagnosis of Idiopathic Epilepsy in a dog (and to a lesser extent a cat) demonstrating:

- 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.

The diagrams below present the diagnostic investigations of generalised seizures and focal seizures. Specific diagnostic investigations are presented below.


Generalised seizures
Abnormal clinicopathological tests
Normal clinicopathological tests
Normal or abnormal neurological examination
Normal CSF, CT and/or MRI
Normal clinicopathological tests
Normal or abnormal neurological Examination
Abnormal CSF, CT and/or MRI
Extracranial disorder (i.e. intoxication, hypoglycemia, hepatic encephalopathy)
Idiopathic epilepsy or cryptogenic epilepsy (residual damage)
Symptomatic epilepsy (i.e. encephalitis, head trauma neoplasia or hydrocephalus)


Focal seizure or focal seizure with secondary generalisation
Normal clinicopathological tests
Normal or abnormal neurological examination
Normal CSF, CT and/or MRI
Normal clinicopathological tests
Normal or abnormal neurological Examination
Abnormal CSF, CT and/or MRI
Idiopathic epilepsy or cryptogenic epilepsy (residual damage)
Symptomatic epilepsy (i.e. encephalitis, head trauma neoplasia or hydrocephalus)

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
- Arterial blood pressure

Investigation of Suspected Intra-Cranial Causes

- Complete haematology
- Comprehensive biochemistry
- Thoacic 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

Management of idiopathic epilepsy often requires a lifetime commitment by the owners. Despite all the time and effort (including financial commitment), a significant proportion of dogs may still continue to have seizures despite treatment. Therefore, proper client education is critical in preparing owners for understating their pet's condition and aims of treatment.

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.

Important information to provide to the owner:

- 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 anti-epileptic 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).

Phenobarbitone

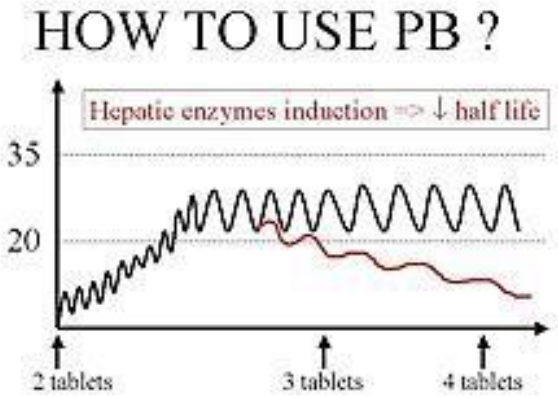
Overview

Phenobarbitone 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. The figure below illustrate the effect of chronic administration of phenobarbitone (PB) and the need to increase oral dosage with time to maintain therapeutic level.



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 194mmol/l (preferably at least 110 to 130mmol/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

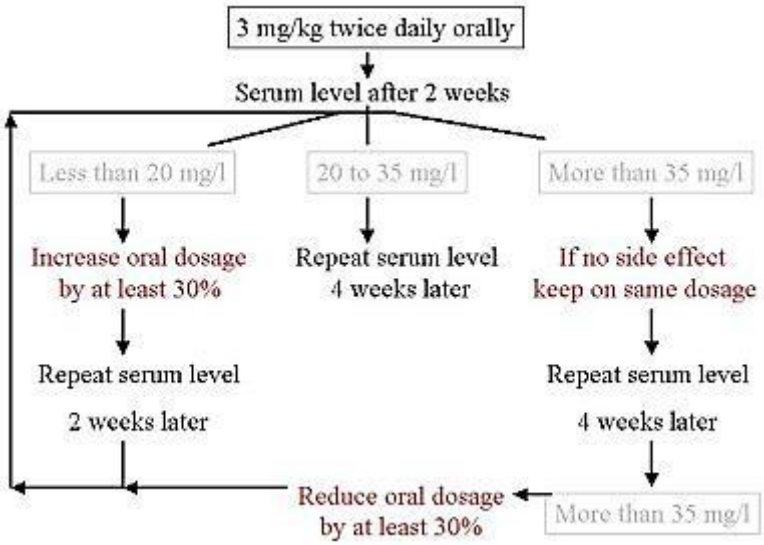
To determine the phenobarbitone blood levels:

- 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).

The figure below summarizes the starting dose of phenobarbitone and how to adapt the oral dosage depending on the initial serum level obtain 2 weeks later after starting treatment.



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 Hepatotoxicit

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

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 imepitoinis 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.

Potassium bromide

Overview

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 mmol/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.

Obtaining potassium bromide

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. Be aware that bromide is very electrochemically similar to chloride, since both are halide ions. As a result, it is important that dogs on bromide therapy should not have their diet altered - a change in salt (ie NaCl) concentration will alter the amount of bromide absorbed from the gastrointestinal tract and excreted in the urine (low salt diets lead to an increase in bromide absorption and retention). In addition, some laboratory biochemistry panels will detect bromide in place of chloride, leading to spurious elevations in chloride levels in patients on bromide therapy.

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 (up to 10% of patients on combination bromide and phenobarbitone therapy, according to one article). 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.

Potassium bromide should never be used in cats as it has been associated with a life-threatening eosinophilic bronchitis that has been fatal in some cases.

Managing refractory seizures

Most epileptic dogs are treated pharmacologically successfully for life with phenobarbitone. However, about 20 - 30% of treated dogs are reported to either be poorly responsive to first line anti-epileptic drug and/or suffer unacceptable side effects and toxicity. In patients with apparent refractory epilepsy, it is essential to search for errors in diagnosis or management that may be responsible for treatment failure. This include considering the following steps:

1. Is the animal having epileptic seizures as opposed to other paroxysmal disorder (e.g. paroxysmal movement disorder)?
2. Is-it idiopathic epilepsy or could there be an underlying cause (metabolic or structural brain disease)?

UNDERLYING MECHANISMS OF PHARMACORESISTANT EPILEPSY

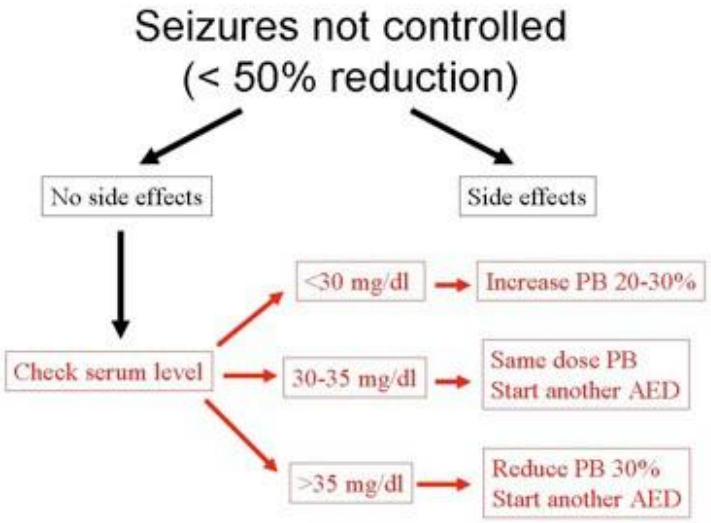
There are three major theories:

- Removal of antiepileptic drugs from the epileptogenic tissue through excessive expression of multidrug transporters (multidrug transporter hypothesis). Recently an over-expression of P-glycoprotein was demonstrated in dogs after increased seizure activity, status epilepticus and cluster seizures. Multidrug transporters such as P-glycoprotein act as drug efflux transporters in the blood brain barrier, limiting the penetration of various lipophilic drugs into the brain. An increase expression of such transporters in the blood brain barrier is thus likely to reduce brain drug levels of anti-epileptic drug.
- Reduced drug-target sensitivity in epileptogenic brain tissue (drug-target hypothesis)
- Change in neuronal network properties

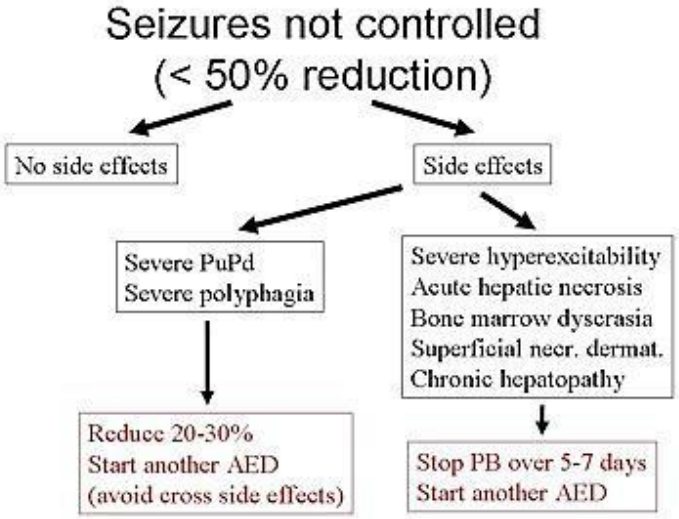
RATIONAL APPROACH TO REFRACTORY EPILEPSY

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:

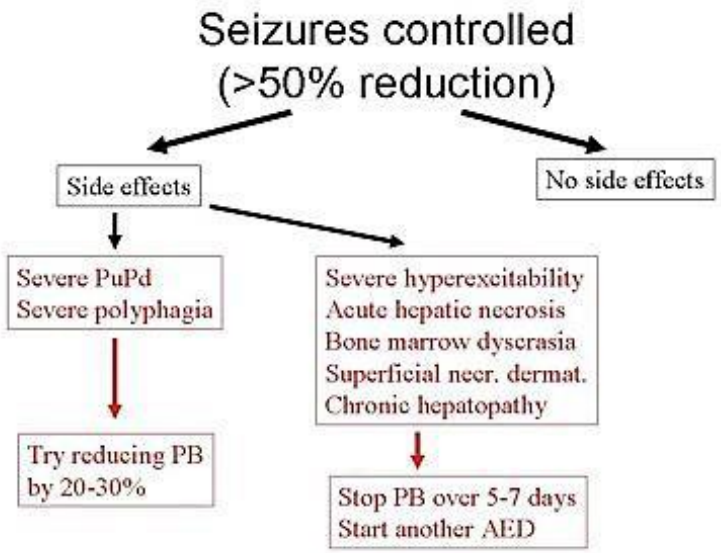
Seizures not controlled but no side effects: Serum phenobarbitone should be checked. If serum level is > 35 mg/dl, another AED should be started, oral phenobarbitone dosage should be slowly reduced (aiming to reach serum level below 35 mg/dl) to limit risk of liver toxicity. If serum level is in the 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 (imipetoin, 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 (imipetoin, levetiracetam, zonisamide, pregabalin)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 such as levetiracetam) while taking the animal off phenobarbitone over 5 -7 days.



Levetiracetam

Levetiracetam appears to have a different mechanism of action when compared to existing antiepileptics, which may prove advantageous in polytherapy. Its unique mechanism of action is mediated by binding to the presynaptic vesicular protein, SV2A, which decreases glutamate neurotransmitter release. 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. The rug is well tolerated with sedation noted as the most common adverse side effect. A new extended release formulation of levetiracetam has been shown to have half-life in excess of 7 hours in dogs following oral administration, giving rise to the potential for once or twice daily administration.

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 (18-28 hours) and high protein-binding affinity (70%). 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, dry eye, ataxia, vomiting 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.

Emergency seizures

Status epilepticus can be defined as continuous seizure activity lasting longer than 30 minutes or the occurrence of two or more seizures without full recovery of consciousness during the inter-ictal period.

However immediate treatment is required in any prolonged seizures and emergency treatment should be administered (where possible) well before the defined 30-minute time.

SUPPORTIVE CARES AT THE TIME OF PRESENTATION

When the dog or cat presents in status epilepsticus consideration must be given to the following factors as a priority:

- Establish intravenous access.
- Maintain patent airway and administer oxygen by face mask or in the absent of gag reflex intubate the patient
- Administer IV NaCl 0.9% with KCl 26 mEq/L at maintenance rate (use of fluid such as Lactate Ringer may result in microprecipitation of intravenous diazepam)
- Maintain normal body temperature as status epilepticus may result in hyperthermia using moist towel. All cooling method should be stopped when rectal temperature reaches 102°F or 39°C as over-shoot hypothermia may occur.

CESSATION OF SEIZURE ACTIVITY

Administration of intravenous antiepileptic medications should be commenced immediately upon attaining IV access in a SE patient. As IV access is not frequently initially available, other routes of administration should be considered. Immediate therapy is indicated based upon acceptance that the duration of SE is linked to neurologic morbidity and that SE may become progressively less responsive to treatment with diazepam.

STEP 1: BENZODIAZEPINES

This class of drugs includes diazepam, midazolam, lorazepam, and clonazepam. They are injectable, potent and fast-acting making them the preferred initial therapy in SE. With their effects only being temporary, a more long acting anticonvulsant will be necessary following their use.
Respiratory depression, hypotension and reduced consciousness are all possible side effects.

Diazepam - 0.5-2.0mg/kg IV up to 20mg maximum dose

Intravenous administration is obviously preferred; however, if intravenous access is not available it may be administered rectally or intranasally. Intramuscular absorption of diazepam is variable thus this route of administration is not recommended. Rectal administration results in adequate absorption with peak plasma concentrations reached within 15 minutes. It is important to note that patients on long-term phenobarbital therapy may require higher doses of diazepam (2mg/kg) due to activation of the liver's hepatic cytochrome P-450 enzyme system resulting in increased metabolism of diazepam and its metabolites. Target plasma concentrations are reached in approximately 10 minutes in animals that are not being treated with phenobarbital (phenobarbitone) and by 20 minutes in animals on chronic phenobarbital therapy.

If one to two doses of diazepam fail to control the seizure manifestation, addition of another, longer-acting anticonvulsant medication should be immediately considered; however, it should be remembered that these drugs can take a short time to become effective. Continued administration of diazepam, in the face of failure to control seizure manifestation, may result in further neurologic compromise to the patient from the seizure activity as well as toxicity from diazepam. It is important to note administration of diazepam in cats has been associated with acute hepatic necrosis. However, this complication has only been reported when diazepam is administered orally thus parenteral administration of diazepam in the emergency situation should not be withheld from feline patients.

If a bolus of diazepam does work but only for a short time, a constant rate infusion should be considered (0.1-0.5 mg/kg/hr) prior to the longer acting anticonvulsant becoming effective. A syringe pump can be used or the diazepam can be diluted in 5% dextrose in water (D5W) such that the total volume administered is equal to the patient's maintenance fluid requirement over the hour. Concerns regarding aqueous solubility, formation of deposits and adsorption onto polyvinyl chloride tubing have been raised. Compatibility should be checked before combining diazepam with any other medication or intravenous fluid as formation of precipitates is common. Never administer if a precipitate forms. Use of midazolam in lieu of diazepam circumvents many of these concerns; however this is far more expensive. If diazepam is used the administration set should be protected from light and changed every 2 hours. Care should also be taken when administering other medications into this line as many medications will cause precipitations to form when combined with diazepam.

A high initial rate is used following a bolus dose and is usually continued for up-to 6 hours before a gradual and tapered (50% every 6 hours) reduction is begun. This approach is useful if SE is due to toxicity where seizures will likely be present for a protracted time period or while awaiting a loading dose of phenobarbital to become effective.

Midazolam - 0.06-0.3mg/kg IM or IV

Midazolam's peak plasma concentration in dogs after IM injection is 15 minutes and its half-life in dogs is 1-2 hours. Midazolam's superior absorption and bioavailability with intramuscular injection when compared to diazepam makes it a feasible alternative when there is no IV access on initial presentation.

STEP 2: BARBITURATES

Following the successful use of benzodiazepines, barbiturates should be considered necessary as long-term maintenance anticonvulsants and can be parenterally loaded to achieve a rapid steady state serum concentration. Loading phenobarbital is usually only performed in those patients that have not previously received this drug or are suspected to have low serum drug levels. If bolus doses of benzodiazepines did not stop the seizure activity or were only temporarily successful, barbiturates become the next therapeutic option. Phenobarbital is the most commonly used barbiturate for acute seizure control. The loading dose of phenobarbital is 12-24mg/kg IV. However, it is recommended to administer smaller boluses (2-4mg/kg), repeating every 20-30 minutes, to effect but not exceeding 24mg/kg over 24 hours. The parenteral form of phenobarbital may be also used intramuscularly which is useful in the initial treatment of a case which does not have IV access. However the distribution of phenobarbital to the CNS and hence its effect may take up to 30 minutes due to its low lipophilicy. Intramuscular administration may avoid the profound respiratory and cardiovascular depression experienced when phenobarbital is administered following benzodiazepines.

Side effects of phenobarbital include respiratory depression, hypotension and sedation. In a SE patient, whose respiratory and cardiovascular function may already be compromised, these side effects could become life threatening, thus monitoring of respiratory and cardiovascular parameters must be continuously performed.

Parenteral use of this drug should be followed by the more routine twice daily oral administration as soon as is possible, to ensure long term control of seizure activity is addressed.

STEP 3: LEVETIRACETAM

If the use of phenobarbital is not successful or is considered inappropriate (e.g., underlying presence of liver disease), the next option is the use of levetiracetam. Levetiracetam (20-60mg/kg IV) is a newer anticonvulsant which has a half-life of 3-4 hours in dogs. Its IV use may be effective for 8 hours at which time it can be repeated. It causes minimal sedation making it desirable in treating the more refractory SE patients that already have an altered consciousness. It is not metabolized in the liver and so represents a more suitable option than phenobarbital for dogs and cats with portosystemic shunts or liver disease. Excretion is purely renal and thus there are minimal interactions with other anticonvulsant medications; however, caution should be used in patients with deficient renal function. Levetiracetam may also have neuroprotective effects, reducing seizure-related brain damage. As for phenobarbital, the oral maintenance use of levetiracetam should follow its parenteral use once SE has been controlled.

STEP 4: SHORT ACTING ANAESTHETIC AGENTS

Status epilepticus that does not respond to a benzodiazepine, phenobarbital or levetiracetam is considered refractory and requires more aggressive treatment. Potential reasons for resistant seizure activity include inadequate anticonvulsant doses, an uncorrected metabolic abnormality or the presence of an intracranial disease, such as a tumor. These patients often represent a difficult therapeutic problem. Short-acting anesthetic drugs are the most commonly used agents for treating resistant SE, as they have a rapid onset of action, short half-lives, and cause reductions in cerebral metabolic rates. These drugs should be used only in an intensive care setting because of the need for continuous blood pressure monitoring and ideally, central venous pressure monitoring.

Propofol 1-2mg/kg IV bolus or 0.1-0.6mg/kg/min titrated to effect, up-to 6mg/kg/hr as a CRI

Propofol acts on the GABA receptor similar to both barbiturates and benzodiazepines and so has anti-convulsant actions as well as being an anaesthetic. It also reduces the metabolic demand of the CNS. The primary side effect of propofol is apnoea, which may result in hypoxemia if not treated appropriately. Thus, if a CRI of propofol is used, adequate airway control, hemodynamic support and possible ventilatory support should be available.

In human medicine, a propofol infusion syndrome has been reported when propofol has been used at high doses (>4mg/kg/hr) or for prolonged periods (>48 hours). Signs of this syndrome include metabolic acidosis, rhabdomyolysis, hyperkalemia, lipemia, renal failure, hepatomegaly, and cardiovascular collapse. While this syndrome has not been reported in veterinary patients the possibility exists, especially in those patients maintained on a CRI long term. It is important to note that propofol is a phenol and thus capable of causing oxidative injury to RBC of the cat resulting in Heinz body formation and hemolytic anaemia.

Ketamine 5mg/kg IV bolus followed by 5mg/kg/hr CRI

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptor antagonists, like ketamine, are able to end the maintenance phase of chronic SE, sometimes called self- sustaining SE. NMDA receptor activation only occurs in later phases of SE, perpetuating the seizure activity, so NMDA antagonists are suspected to be beneficial during prolonged or refractory SE. Ketamine also may have neuroprotective effects by inhibiting NMDA receptor-mediated excitotoxicity associated with prolonged seizure activity; however there is also some evidence that excessive antagonism of the NMDA receptors can be detrimental. Although the use of ketamine has been documented in a dog with SE, there are currently no clinical studies documenting the effectiveness or safety of ketamine CRIs in treating veterinary patients.

STEP 5: INHALANT ANAESTHESIA

Inhalant anesthesia is considered a last resort in refractory SE. Not all volatile anesthetics are appropriate in managing the SE patient. For example, enflurane may increase seizure activity. Isoflurane and sevoflurane may attenuate seizure activity as has been shown in cats with experimentally induced seizures. The utility of this approach is in the cessation of the physical manifestations of SE while a maintenance anticonvulsant takes effect. Maintaining a patient on inhalant anesthetics requires intensive monitoring and mechanical ventilation. During this time, phenobarbital, levetiracetam or bromide should be dosed at a loading dose to achieve steady state. at which time the anesthesia can be withdrawn to assess seizure control

STEP 6: RECOVERY/MAINTENANCE

Some patients will display marked agitation upon recovery. Use of dexmedetomidine as a CRI (0.1 to 1.0 mcg/kg/hour) has been reported to help manage this issue. However, caution must be used as dexmedetomidine may cause bradycardia, arrhythmia (AV block), decreased respiration and hypothermia which can be problematic in the SE patient; therefore the dose should be adjusted following careful monitoring.

Vital parameters including heart rate, blood pressure, ventilation and body temperature should continue to be monitored and serial neurologic examinations performed until the patient is mentally alert and mobile. The combination status epilepticus and the previously mentioned medications can result in marked cardiovascular and respiratory depression as well as hypothermia. It is imperative that the clinician monitor parameters to ensure systemic support is continued as needed for a complete recovery.

Once seizure activity has been controlled and systemic stabilization has been ensured, a maintenance antiepileptic drug (AED) will need to be considered. In a naïve patient phenobarbital may be used as the sole medication. In a patient with a history of SE it is recommended that the patient be loaded so that steady state serum levels are reached as quickly as possible. The instructions for loading phenobarbital have been described above. If the animal was on phenobarbital prior to the episode of SE, two options exist. If the animal's serum phenobarbital level is low, an increase in dose may be indicated. If the serum level is well within the therapeutic range, is approaching toxic levels, or if the patient is displaying adverse effects an additional AED may be added.