Acute Seizure Management: What Do We Really Know About the Drugs We Give?
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A seizure is the outward, observable outcome following a transient paroxysmal event in the brain. This paroxysm, or misfire, can be a single event or repetitive, resulting in an epileptic syndrome. Acute seizure management is aimed at stopping both the physical manifestation as well as the electrical synchronization occurring in the brain. Let’s review the seizure phenotypes and parts of a seizure before we dive into seizure treatment options.

Definitions
There are three parts of a seizure to be familiar with: 1) Pre-ictal phase 2) Ictus and 3) post-ictal phase. During the pre-ictal phase the animal may have a sensation of an impending change, which may manifest in hiding or seeking behaviors with the owners. Physical abnormalities, including vomiting or nausea occur within seconds or minutes prior to the onset of the seizure. During ictus, or the seizure often an autonomic and somatic component can be identified. Autonomic signs may include: salivating, urinating, defecating, additional vomiting or eyes dilating. Somatic activity is what we most commonly associate with a seizure and may manifest as one part of the body twitching such as seen with a partial seizure, or tonic-clonic limb movements involving all four limbs as seen with a generalized seizure. The post-ictal phase may last for seconds to hours, and may result in blindness, ataxia, confusion or aggression. Ictus typically lasts seconds to 3 minutes. Any seizure longer than 5 minutes is considered status epilepticus.

Prolonged seizures can result in hypertension, tachycardia, acidosis and hyperthermia with secondary neuronal cell death and hypoxia. These changes negatively affect the brain and may have systemic effects as well. The goals of acute seizure management are to stop the seizure as quickly as possible thereby limiting secondary brain and extra cranial organ damage.

Drug interventions
Benzodiazepine
Benzodiazepine drugs (Diazepam, Midazolam, Lorazepam) were introduced in the 1960s for human status epilepticus. A recent human meta-analysis identified that benzodiazepines are the “best” first line IV drugs and identified the therapeutic concentration to be between 150-300 ug/ml.1 To date, there have been no any veterinary studies identifying which drug is ‘best’ for acute seizure management. We’ve always used benzodiazepines so we continue to do so. Several studies have been published in veterinary medicine addressing different ways to use benzodiazepine drugs in acute seizure management. 2–6 Home care with liquid rectal diazepam is often recommended for patients at risk for cluster seizures however compounded suppositories are not currently recommended.3,7 Rectal midazolam, at the doses tested, was not absorbed in sufficient amounts to make it useful for clinical patients and rectal lorazepam is not used because lorazepam metabolites are not active. We also know that chronic phenobarbital use reduced plasma concentrations of diazepam. With this knowledge we recommend dosing rectal diazepam at 1-2 mg/kg if the patient is receiving chronic phenobarbital therapy. Other routes available for benzodiazepine use include intranasal and intramuscular. Intranasal diazepam, using an atomizer, resulted in detectable levels in about 2.5 minutes which makes this drug a viable alternative for at home anticonvulsant care. Intranasal lorazepam reached the target serum concentration in all dogs in less than 9 minutes however the delay may render this drug clinically less useful.6 Intramuscular midazolam is preferred over intramuscular injection of diazepam however the time to peak concentration was less than 10 minutes which may still be too long in the acute setting to be clinically useful.4

Benzodiazepine summary:
1. Diazepam – may be given rectal, intravenous or intranasal but NOT intramuscular
2. Midazolam – may be given intramuscular, intravenous but NOT rectally
3. Lorazepam – may be given intravenous or intranasal but NOT rectally

Levetiracetam
Levetiracetam is still considered a new anticonvulsant drug, however its use has been documented in veterinary medicine since 2004. (ACVIM Forum Abstract 2004) It is considered a relatively safe drug, with few reported side effects. This drug is typically used as an alternative to intravenous benzodiazepine therapy for acute seizure management at doses ranging from 30-60 mg/kg IV.8 The bioavailability of intramuscular levetiracetam is high, however the time to maximal concentration is about 40 minutes which limits its usefulness for intramuscular administration in the acute phase.9 Peters et al evaluated rectal levetiracetam and identified serum concentrations within the human therapeutic reference interval, however the first sampling time was 10 minutes therefore it is unclear if this drug will be useful in acute seizure management.10 Pulse levetiracetam therapy may be useful for dogs and cats at risk for cluster seizures. During pulse, patients are administered levetiracetam every 8 hours until the cluster seizure abates after which time the drug is discontinued. Pulse therapy can be performed with per os administration at home, or intravenous administration in hospital.
Propofol
The common anesthetic drug propofol has anticonvulsant properties however there are a small number of published studies addressing this use in veterinary medicine. This drug is only recommended for intravenous use. In a study by Steffen et al acute seizure control was obtained in most animals with intracranial diseases induced seizures.\footnote{Steffen F, Grasmueck S. Propofol for refractory seizures in dogs and a cat with intracranial disorders. J Small Anim Pract. 2000;41(November):496-499.} Care must be exercised when using propofol due to its respiratory suppressive effects. Occasionally, intubation may be required if apnea is encountered during bolus therapy. Propofol withdrawal may result in distal limb twitching which may be difficult to distinguish from seizure activity. EEG is often used in our practice to differentiate between ictus and propofol withdrawal however other clinical clues such as mental responsiveness and response to tactile stimuli may be utilized if an EEG is not available. Finally, extended exposure in cats to propofol may result in Heinz body anemia therefore a CBC analysis is recommended every 24 hours during constant rate infusion of propofol with cats.

Summary
Benzodiazepine drugs are the recommended first line of anticonvulsant therapy for dogs and cats. The “best” benzodiazepine drug has yet to be determined through objective assessment. If seizures do not stop after 2 doses, intravenous levetiracetam should be administered and lastly, propofol if seizures persist.

References
Canine meningoencephalitis is a general term, used to collectively describe inflammation in the brain and lining, or meninges, of dogs. Although infectious meningoencephalitis can occur, the majority of dogs have a non-infectious, inflammatory disease. Infectious disease, when present, is typically identified in CSF, serology, blood or urine culture, or organism identification in the peripheral system. The focus of this talk will be non-infectious canine meningoencephalitis. Terminology is important when discussing inflammatory brain disease so let’s start here.

Table 1: Terminology

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Definition</th>
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<tr>
<td>Meningitis</td>
<td>Inflammation of the lining of the brain (meninges)</td>
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<tr>
<td>Encephalitis</td>
<td>Inflammation of the brain parenchyma</td>
</tr>
<tr>
<td>Myelitis</td>
<td>Inflammation of the spinal cord parenchyma</td>
</tr>
<tr>
<td>GME</td>
<td>Granulomatosus meningoencephalomyelitis</td>
</tr>
<tr>
<td>NME</td>
<td>Necrotizing meningoencephalitis</td>
</tr>
<tr>
<td>NLE</td>
<td>Necrotizing leucoencephalitis</td>
</tr>
<tr>
<td>EME</td>
<td>Eosinophilic meningoencephalitis</td>
</tr>
<tr>
<td>MUO/MUE</td>
<td>Meningoencephalomyelitis of unknown origin/etiology</td>
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When histopathology is performed (using brain biopsy or necropsy) the inflammatory brain disease can be further classified as GME, NME, NLE or EME. Often histopathology is not obtained ante mortem therefore the term meningoencephalomyelitis of unknown origin (MUO) is commonly used to describe a dog with evidence of inflammatory brain disease on MRI and CSF analysis, without a histopathologic diagnosis. A diagnosis of MUO denotes a dog who has been diagnosed ante mortem with inflammatory brain disease without evidence of infectious etiology.

Clinical picture

The onset of clinical signs secondary to MUO may be acute or chronic, and result in focal or multifocal lesion localization. Subtle differences in clinical presentation between GME, NME and NLE are reported however extensive crossover in affected breeds, age at onset and sex make positive identification of these diseases without histopathologic examination impractical. Therefore, any dog, with acute or chronic onset of neurologic signs, with focal or multifocal lesion localization should have MUO added to the differential diagnoses list.

Recently, genetic markers were identified in Pug and Maltese dogs which may indicate a risk for development of MUO in those breeds. Practically speaking these breeds may be at increased risk for the development of MUO if they are exposed to a trigger. The identified gene alteration in Pug and Maltese dogs is the same mutation identified in human Multiple Sclerosis (MS) suggesting a shared pathway for disease. Triggers such as exposure to second hand smoke, UVB radiation, obesity, dietary restrictions and population density have been linked to the development of MS in humans and EAE of mice. This association is currently under investigation for dogs diagnosed with GME, NLE and NME.

Diagnosis

MUO is a clinical diagnosis which must be supported by diagnostic investigation. Magnetic resonance imaging (MRI) focused to the area of neuroanatomic lesion localization, cerebrospinal fluid (CSF) analysis and geographically specific infectious disease testing are utilized to support a diagnosis of MUO. To diagnose MUO, the following criteria have been proposed: 1) Multifocal neuroanatomic lesion localization; 2) Age > 6 months; 3) Intra-axial hyperintense lesions on T2-weighted MRI; 4) Pleocytosis with > 50% mononuclear cells and increased protein concentration in CSF and 5) Negative testing for geographic-specific infectious diseases.

Treatment

Standard initial treatment is immunosuppressive glucocorticoid therapy (1 mg/kg twice daily prednisone or prednisone equivalent) because of ease of administration for owners, good penetration through the blood brain barrier and comparatively low cost. A slow taper over months is recommended, however some animals require medication for life. Immunosuppression with a standardized single agent glucocorticoid protocol resulted in slightly less than 50% of patients obtaining a normal CSF analysis at 1 month. If glucocorticoid therapy is intolerable to dog or owner, numerous other protocols may be considered. Additional immunosuppressive treatment is dependent on patient health status, owner socioeconomic status and clinician preference. Alternative immunosuppressive therapies include Cytosine arabinoside (variable protocols), Cyclosporine (range of doses), Lomustine (range of doses), Procarbazine (25-50 mg/m2 once daily orally), and Azathioprine (2 mg/kg once daily orally, then tapered).

Prognosis
Median survival published in the literature range from 26 days to >1800 days. Identification of reliable prognostic indicators has been the focus of many studies. Unfortunately comparison across studies is difficult because inclusion criteria, drug protocols and endpoint measurements differ between studies. In our practice we typically consider the prognosis guarded-to-fair based largely on the dog’s response to immunosuppression.

Future studies are focused on identification of triggers in ‘at risk’ dogs, and prognostic indicators once affected. Large multi-center prospective studies evaluating standardized drug protocols will be critical in the generation of appropriate treatment recommendations.

References
The vestibular system is responsible for maintaining balance. It coordinates movement of the head, eyes and body so that they work together to oppose gravity and maintain correct posture.

**Anatomy and function**

The vestibular system is composed of a peripheral portion and a central portion. The peripheral portion is made up of the receptor organs and an afferent cranial nerve (CN VIII) that conveys information to the brain stem. The central portion is comprised of several nuclei and processing centers within the brain stem and cerebellum.

**Peripheral anatomy**

The primary sensory organs for the vestibular system are contained within the three semicircular canals, plus two additional vesicles, the utricle and the saccule. These 5 endolymph filled organs are connected with each other and with the cochlea. They are located within osseous chambers in the petrous temporal bone, and together with the cochlea comprise the inner ear. The receptor cells are hair cells that are sensitive to motion and position of the head with respect to gravity. The vestibular nerve joins with the cochlear nerve to become CN VIII. This nerve enters brainstem through the internal acoustic meatus.

**Central anatomy**

Neurons within CN VIII synapse with cells in nuclei in the rostral medulla (4 vestibular nuclei on each side of the brain stem) and cerebellum. Vestibular tracts extend rostrally to the midbrain to influence eye movements and caudally to influence muscles in the limbs and neck. The cerebellum is also considered part of the central vestibular system. Information from the vestibular nuclei in the brainstem can be sent to the cerebellum, and the cerebellum also influences the vestibular nuclei in a relay.

**Clinical signs of abnormal vestibular function**

When vestibular input is disrupted the animal receives incorrect information about its place in the world. Eye movements, head position, balance and coordination may all be disrupted. All of the following are evidence of vestibular dysfunction.

1. **Head tilt** – the head is tilted to the right or left. A head tilt can be identified because the animals’ eye sockets appear not to be parallel to the floor. This is NOT the same as a head turn, in which the eyes are parallel to the floor but the head is turned back towards the left or right side. Often the head tilt is permanent even after resolution of the underlying disease.
2. **Circling** – circles tend to be tight and continuous, but may be wider depending on the stage of the disease.
3. **Falling/rolling** – the animal tends to fall or stagger over to one side and in severe cases may be unable to rise and roll over continuously in one direction.
4. **Spontaneous nystagmus** – abnormal eye movements in which there is a slow movement in one direction followed by a fast “flick” in the opposite direction. Spontaneous nystagmus is characterized as follows:
   a. **Direction**: nystagmus can be horizontal – right or left, rotary or vertical. The direction of horizontal nystagmus is named for the direction of the fast phase.
   b. **Positional vs. non-positional** – in positional nystagmus, the character of the nystagmus changes depending on the position of the animal (for example the nystagmus might be vertical when the animal is in dorsal recumbence but rotary when standing). In non-positional nystagmus the character of nystagmus is the same regardless of head or body position.
   c. **Conjugate vs. dysconjugate** – in conjugate nystagmus (by far the most common) the two eyes move synchronously with one another, while in dysconjugate nystagmus the two eyes move differently with respect to each other.
5. **Positional Strabismus** – abnormal position of the globe when the neck is extended dorsally.
6. **Ataxia** – incoordination of the limbs, trunk and head. Animals with a vestibular ataxia will stagger, typically to one side, with their entire body. When severe the ataxia may prevent the animal from walking.

**Neuroanatomic localization**

<table>
<thead>
<tr>
<th></th>
<th>Peripheral (CN 8)</th>
<th>Medulla oblongata</th>
<th>Cerebellum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head tilt</td>
<td>+ (ipsilateral)</td>
<td>+ (ipsilateral)</td>
<td>+ (contralateral)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ataxia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Postural reaction deficits</td>
<td>-</td>
<td>+ (ipsilateral)</td>
<td>Unusual, but possible</td>
</tr>
<tr>
<td>Paresis</td>
<td>-</td>
<td>+ (ipsilateral)</td>
<td>-</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-----------------</td>
<td>---</td>
</tr>
<tr>
<td>Decreased mentation</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hypermetria</td>
<td>-</td>
<td>-</td>
<td>+ (ipsilateral)</td>
</tr>
<tr>
<td>Intention tremors</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Other cranial nerves</td>
<td>+/- (CN 7 sometimes)</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Differential diagnoses

The most common differential diagnoses for dogs and cats diagnosed with **peripheral** vestibular disease are:

1. Idiopathic vestibular disease of old dogs – animals typically present with peracute onset severe vestibular signs in dogs over 7 years of age. The dogs often vomit first and then show severe difficulty walking with nystagmus. Although the appearance is very severe, they usually improve with supportive care alone.
2. Otitis media/interna – ear infections affecting the vestibular apparatus will result in signs of vestibular dysfunction. Appropriate antimicrobials or antifungals may resolve the infection but repeated infections are best treated with surgical flushing and removal.
3. Hypothyroidism – Hypothyroidism may cause demyelination and axonopathy via one of these mechanisms: 1) accumulation of mucinous deposits resulting in nerve entrapment 2) demyelination secondary to Schwann cell defect, 3) vascular nerve damage secondary to hypothyroid induced dysfunction of BBB 4) disruption of axonal transport. Signs may be limited to the vestibular system or involve other peripheral nerves with or without concurrent systemic signs of hypothyroidism. Treatment with hormone replacement will improve, but rarely eliminate, clinical signs.
4. Neuritis – CN VIII is one of the few cranial nerves that communicates with the meninges. As a result, meningoencephalitis may result in neuritis of CN VIII as well. Diagnosing neuritis can be challenging if meningoencephalitis is not evident, however typically a rapid response to immunosuppression is seen with high dose prednisone therapy.

The most common differential diagnoses for dogs and cats diagnosed with **central** vestibular disease are:

1. Meningoencephalitis/encephalitis – this is most commonly an immune mediated disease in dogs and 50% of the time in cats. Therefore treatment is aimed at immunosuppression. If infectious, appropriate antimicrobial/antifungal/antiparasitic therapy is required instead of immunosuppression. See notes on Canine meningoencephalitis for further details.
2. Neoplasia – Depending on the tumor type, medical and surgical intervention may be possible. Medical therapy involves supportive care (anti-nausea medication, anti-inflammatory medication) and physical care (slings to help the dog walk, avoiding stairs and limiting rough play on hard surfaces to limit injury).
3. Vascular disease – ischemic infarcts are more common than hemorrhagic infarcts in dogs and cats and are more common in the cerebellum. MRI is often most helpful to obtain a diagnosis. 50% of the dogs with vascular disease on MRI have been shown to have an underlying cause which would predispose them to thrombi or coagulopathy. These may include: renal disease, platelet disease/dysfunction, hypertension, cardiac disease, or endocrine disease (thyroid or adrenal). If an underlying cause is found, treatment should be directed at improving this disease as a means to reduce the chance of additional vascular events occurring. The remaining 50% of dogs do not have an identifiable cause and are therefore treated symptomatically.

### Case examples

- **7 year old FS German Shepherd dog**
  - 9 year old FS Chow Chow
  - 3 year old FS Brittany spaniel