Practical Neurology
Seizure Disorders
The most common Neurologic Problem in Small Animal Medicine
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Types of Seizures

Generalized Seizure
• Used to be called “grand mal”
• Usually tonic-clonic
• Most common kind of seizure
• Usual loss of consciousness
  – Sometimes partially conscious
• First phase tonic
  – Stiff, opisthotonus
  – May be cyanotic
  – Vocalize, salivate, urinate, defecate
  – A minute or so
• Second phase clonic
  – Paddling or jerking of the limbs
  – Chewing movements
  – May be several minutes

Types of Seizures

Focal (Partial) Seizure
(2 kinds)
• Simple focal seizure
  – Consciousness not impaired
• Complex focal seizure
  – Consciousness is altered
  – Unprovoked aggression
  – Canine rage syndrome
  – Aka Episodic dyscontrol
  – Irrational fear
  – Psychic seizure
  – Aka Psychomotor seizure

Types of Seizures

Focal (Partial) Seizure
• Any body part may be involved
• Depends on the seizure focus location in the cerebrum
  – Facial spasms
  – Head movements
    – “yes” or “no”
  – Fly biting
  – Repetitive limb movement
  – Licking or chewing a single area
  – Hypersalivation
  – Vomiting, diarrhea, abdominal pain
• Limbic epilepsy

Types of Seizures

Focal/Partial seizures can progress to Generalized Seizures
• This can be a clue in the history that distinguishes seizure from other episodes of collapse
  – Starts with a twitching limb or turning head
  – Progresses to generalized seizure
### Differential Diagnosis

**Episodes resembling seizure**
- Syncope
- Narcolepsy
- Stereotypic Behavior
- 4 kinds of tremor
- 3 kinds of ataxia
- Rapidly progressive weakness
- Encephalopathy
- Active sleep
- Pain
- Hyperviscosity Syndrome

### Differential Diagnosis

**Seizure**
- Often spontaneous onset
  - Exercise triggers syncope & progressive weakness
  - Excitement triggers narcolepsy
- Usually self limiting

### Differential Diagnosis

**Seizure**
- Often composed of 3 stages
  - **1 - Pre-ictal** – 2 parts
    - Prodrome – hours – normal EEG
    - Long term indication
    - Restless, vocalizing
  - **Aura** – minutes – abnormal EEG
    - Initial sensation of seizure before observable signs
    - Hiding, agitation, seek owner
  - **2 - Ictal** – the seizure (ictus)
  - **3 - Post-ictal** – minutes to days
    - Transient abnormalities in brain function
    - Disorientation
    - Restlessness
    - Ataxia
    - Blindness
    - Deafness

### Differential Diagnosis

**Syncope**
- Partial or complete loss of consciousness (confusion)
- Short duration (< 1 minute)
- Lack of clonus, but can have tonic like phase
- Lack of post ictal signs
- Often associated with exercise
- How do you tell the difference?
- Confirmed by cardiac work-up

### Differential Diagnosis

**Narcolepsy**
- Flaccid – no tonic phase
- Loss of consciousness
- Precipitated by excitement
  - Most common incitor?
  - Food/eating
Differential Diagnosis
Stereotypic Behavior
• Repetitive bizarre behavior
  – Tail chasing
• Can usually be distracted
• No pre-ictal or post-ictal phase

Differential Diagnosis
Rapidly Progressive weakness
• Myasthenia gravis
• Exercise induced collapse
• Gradually precipitated by vigorous activity
• May recover fully with time
• No loss of consciousness
• May show postural tremors which might be confused with muscle contractions

Differential Diagnosis
Encephalopathy
• No distinct pre-ictal, ictal and post-ictal phases
• Prolonged neurologic signs
  – Disorientation
  – Ataxia
  – Blindness
  – Abnormal behavior
• Cerebral or hepatic
• Encephalopathy leading to seizures can confuse the distinction

Differential Diagnosis
Active Sleep
• Twitching
• Paddling
• Vocalizing
• No post-ictal signs upon waking

Differential Diagnosis
Pain
• Especially neck pain
• Muscle rigidity
• Stiffness
• Crying
• Consciousness not impaired

Differential Diagnosis
Hyperviscosity
• Polycythemia
• High triglycerides
Epilepsy
• Recurrent seizures over time
• A syndrome, not a disease

Different from Provoked seizures
• Aka reactive seizures
• Secondary to metabolic or brain disease, at the time of insult
• Can resolve with underlying cause
  – Hypoglycemia
  – Hypocalcemia
  – Toxicity
  – Trauma

Epilepsy
• Idiopathic epilepsy
  – Aka primary epilepsy
  – No identifiable cause
  – Onset young adult
  – Normal between seizures
    • “well dog with seizures”
  – Normal bloodwork and neurologic exam
  – Neuro exam can be abnormal during post-ictal stage
  – Anticonvulsant therapy can also affect neurologic exam

Epilepsy
• Symptomatic epilepsy
  – Aka secondary epilepsy
  – Identifiable cause of seizures over time
    • Intracranial
      – Congenital storage diseases
      – Hydrocephalus
      – Neoplasia
      – Infectious
      – Inflammatory
      – Trauma
      – Vascular/ischemia
    • Exocranial
      – Hepatic encephalopathy
      – Insulinoma

Epilepsy
• Symptomatic epilepsy
  – Suspect if onset < 1 yrs or >5 years
  – Suspect if focal seizures
  – Sudden onset of cluster seizures
  – Interictal abnormalities on bloodwork or neuro exam
    • “sick dog with seizures”

Breed Predispositions
Fly snapping seizures
• Cavalier King Charles Spaniel

Canine Rage Syndrome
• Springer Spaniel

Head Movement partial seizure
• Boxers and Bulldogs – “no”
• Doberman Pinschers – “yes”

Exercise induced collapse
• Labrador Retriever

Breed Predispositions
Idiopathic epilepsy
• Beagle, Belgian tervuren, Keeshond, Dachshund, GSD, Labrador retriever, Golden retriever, Collie

Status epilepticus
• Labrador retriever
• Large dogs

Narcolepsy
• Rottweiler
• Tail Chasing
• Bull terrier
Working Up the Seizure Patient

- Physical Exam
- Neurologic Exam
  - Avoid post-ictal period
  - Impossible to evaluate if groggy due to anticonvulsants

Working Up the Seizure Patient

- Laboratory Evaluation
  - CBC, profile (TG, Ca), electrolytes
  - Thyroid panel
    - TSH, T4, freeT4
    - hypoT4 associated with seizures
    - Phenobarbital can suppress thyroid function
  - Bile Acids if indicated
    - Young animals
    - High liver enzymes, low albumin, low BUN, abnormal cholesterol, low glucose
    - Yorkies, Maltese
  - Blood lead if indicated
  - TG/chol if indicated - lipemic

Working Up the Seizure Patient

- Advanced Diagnostics
  - CSF tap
    - Prior to antibiotic, antifungal or anti-inflammatory therapy
    - Easy in any practice with gas anesthesia and a spinal needle
  - Referral for CT or MRI
    - Interictal neurologic deficits
    - Focal/partial seizures
    - < 1 year and normal bile acids
    - > 5 years
    - Any cat
  - EEG

Seizure Treatment

When to Treat??

- Single seizure not treated unless status epilepticus
- Provoked seizures not usually treated unless prolonged or severe
- Cluster seizures should be treated aggressively
- Epileptic dogs are better controlled long term when treated early
- Seizures that last longer than a minute or two should be treated
- More than one mild seizure every 2 months should be treated

Seizure Treatment

Client Education

- Medications must be given daily, for life
- Explain side effects & drug interactions (handouts)
- Missed dose should be given as soon as remembered, then back on schedule with next dose
- Owner seizure log – date, time, description, duration
- Dose determined over time by blood tests
- Dose may increase or decrease over time
- Drugs will not reach full effect for weeks to months
- Initial side effects often subside with time

Seizure Treatment

Therapeutic Drug Monitoring

- When steady state achieved after initial treatment
- When steady state achieved after changing dose
- Immediately after loading dose
- When seizure control is suboptimal
- Periodic monitoring, for pre-emptive dose changes (q6-12 months)
  - Induction of liver enzyme can increase PB metabolism rate
  - Prevent poor episodes of control
  - Minimize side effects
Seizure Treatment

Therapeutic Drug Monitoring
- Other drugs added (Phenobarbital)
  - Organophosphate pesticides
  - Ketoconazole
  - Other narcotics
  - Phenothiazines
  - Anithistamines
  - Chloramphenicol
  - Corticosteroids
  - Doxycycline
  - Beta blockers
  - Theophylline
  - Metronidazole

Seizure Treatment

Anticonvulsants
- Dogs
  - Monotherapy
    - Phenobarbital
    - Bromide
  - 2nd line drugs
    - Bromide
    - Phenobarbital
    - Gabapentin
    - Zonisamide
    - Levetiracetam (Keppra)
  - 3rd line drugs
    - Clorazepate
    - Felbamate

Seizure Treatment

Anticonvulsants
- Cats
  - Monotherapy
    - Phenobarbital
  - Ancillary drugs
    - Diazepam
    - Bromide
    - Not much information on other ancillary drugs

Seizure Treatment

Phenobarbital
- Half life 40-90 hrs
- 5 half lives to steady state
- Steady state in 10-15 days
- Initial dose
  - 1-2 mg/lb PO BID in dogs
  - Lower if liver disease
  - 1 mg/lb PO BiD in cats
- Check levels in 2-3 weeks
  - Don’t use SST
  - Goal is 20-40 ug/ml
  - If control suboptimal, push >30
  - Timing with respect to dose doesn’t matter 91% of the time

Seizure Treatment

Phenobarbital
- Side effects
  - Induction of liver enzymes
  - Liver toxicity in dogs only
    - Risk greater if TDL > 35 ug/ml
    - Risk greater with other drugs
    - Bile acids q6-12 months to monitor for toxicity
    - If caught early, toxicity is reversible
  - Altered thyroid tests
    - Decreased T4, fT4
    - Increased TSH
    - No clinical hypothyroidism
  - PU-PD
    - Polyphagia and weight gain
    - Increased panting
    - Non-regenerative anemia
    - Dermal necrosis
Seizure Treatment

**Bromide**
- Na or K bromide
  - KBr preferred for heart disease
  - NaBr preferred for Addison’s Dz
- Added to phenobarbital when TDL 20-35 ug/ml does not achieve control
- Half life 24 days in dogs
- Steady State 10-16 weeks in dogs
- **Initial Dose**
  - KBr 20-35 mg/kg PO SID or divided BID
  - NaBr 17-30 mg/kg PO SID or dBID
  - Higher if on diuretics
- Half dose for patients with renal failure
- Loading dose for cluster seizures
  - 400-600 mg/kg
  - Divided into 4-10 doses over 1-5 days (divide BID-QID)
  - Hospitalize the patient
  - If obtunded or anisocoria, skip & resume when alert
  - Start initial dose next day

- **Check level**
  - One week after loading
  - 3 & 6 months after maintenance dose
  - Timing of sample unimportant
  - Ideal range 1-3 mg/ml
  - Can push to 4 when control suboptimal and phenobarbital >35
  - If adequate control, phenobarbital can be reduced and eliminated over 4 months when Br > 1.5 mg/ml
- **Side effects**
  - Reversible pneumonitis in cats
  - Way high serum Cl results
  - Dose dependent, resolve with time
    - Rear limb stiffness and ataxia
    - Sedation
    - GI irritation
      - Vomiting, esophagitis, constipation
      - Capsules can help
      - Follow capsules with water
      - Give with food
      - Try NaBr

- **Levetiracetam (Keppra)**
  - Half life 4 hours in the dog
  - Despite the short half life, antiseizure effects persist after serum levels fall off
  - Initial dose 20 mg/kg PO TID
  - Side effects uncommon
  - $$$$$
### Seizure Treatment

**Gabapentin**
- Half life 3-4 hours in the dog
- Initial dose 100-300 mg TID
  - Increase every 1-2 weeks until control
  - Up to 1200 mg TID
  - Reduce dose if renal disease
- Or 25-60 mg/kg divided TID-QID
- Do not give within 2 hours of antacids
- Side effects uncommon
  - Little sedation
  - Opiates increase effectiveness and side effects
  - False positive proteinuria on dipstick
- $$$$$

**Zonisamide**
- Half life 15 hours in the dog
- Initial dose 10 mg/kg PO BID
- Therapeutic range for people
  - 10-40 mg/L
- Side effects uncommon in people
  - Drowsiness
  - Ataxia
  - GI upset
  - Known teratogen in dogs
  - Allergy = a sulfonamide
- $$$$$

**Felbamate**
- Half life 5-14 hours in the dog
- Initial dose 15 mg/kg BID-TID
  - Increase every 2 weeks until control
  - Up to 70 mg/kg TID
  - May need to increase with time due to hepatic enzyme induction
- Steady state in 4-6 days
- TDL 15-100 mcg/ml
- Side effects uncommon
  - Little sedation
  - Nervousness at high doses
  - Hepatotoxicity esp. with phenobarbital
- $$$$$

**Clorazepate**
- Can add to phenobarbital and/or bromide in dogs
- Initial dose 0.5-1 mg/kg PO TID
  - SR available but still given TID
- Serum levels often decrease over time
  - Dose increases often necessary
  - Ineffectiveness due to tolerance can occur
- Do not give within 2 hours of antacids
- Side effects
  - Sedation and ataxia
  - Can increase phenobarbital levels
  - Monitor levels closely
  - Monitor for side effects
  - Enhances effects of narcotics
  - Exacerbates open angle glaucoma
  - Liver dz
  - Exacerbates fear induced aggression
- $$$$$

### Monitoring
- CBC, profile, electrolytes q 6-12 months
- Liver enzymes will be high if on phenobarbital
- Does not indicate toxicity
- TDL q 6-12 months
- Bile acids q 6-12 months
- Phenobarbital
- Felbamate
- Wean off these drugs if bile acids begin to increase
- Decrease by 25% each month for 4 months
Seizure Treatment

Drugs not indicated
- Primidone
  - Efficacy similar to phenobarbital
  - Greater risk of liver disease
  - No reason to use it in dogs
  - Toxic to cats
- Short elimination half life
  - Phenytoin (Dilantin)
  - Carbamazepine (Tegretol)
  - Valproic acid
  - Ethosuximide

The Refractory Patient

1. Repeat TDM for phenobarbital and bromide
- Phenobarbital 30-35 ug/ml
- Bromide 2-4 mg/ml
- This monitors compliance

2. Repeat the work-up for underlying cause
- Neurologic exam
- CBC, profile, electrolytes, UA
- Thyroid panel
- Bile acids, TG, blood lead if indicated

3. Consider other causes of episodes of collapse
- Syncope, narcolepsy, behavior, tremor, ataxia, weakness, encephalopathy, active sleep, pain, hyperviscosity

4. Add 2nd or 3rd line drugs
- Keppra, gabapentin, zonisamide
- Clorazepate, felbamate

5. Advanced Diagnostics – do or repeat
- CSF tap
- Chest x-rays, abdominal US
- Refer for CT or MRI if possible

6. Refer for experimental therapies
- Vagal stimulator placement

Emergency Treatment

- Status epilepticus
  - Continuous seizure lasting > 5 min
  - Multiple discrete seizures without full recovery between
  - Seizure >30 min is deadly
    - Hypoxia, hyperthermia
  - Cluster seizures
    - Aka serial seizures, acute repetitive seizures
    - More than 3 seizures in 24 hours

Seizure Treatment

Emergency Anticonvulsants
- Diazepam
- Phenobarbital
- Propofol
- Pentobarbital
- Boluses or CRI

Diazepam (5 mg/ml)
- Half life
  - 2-4 hours in dogs
  - Long enough for maintenance in cats
  - But can cause hepatic necrosis in cats
- Boluses IV or per rectum
  - 0.5-1 mg/kg IV (1-2cc per 20 lbs)
  - Up to 3 boluses
  - Owners can do per rectum at home
- CRI if boluses not effective
  - 0.5-2 mg/kg/hr in DSW or 0.9% NaCl
  - Put 150 ml fluids in the Buretrol
  - Add 7.5-30cc diazepam to the Buretrol
  - Administer at 1 ml/lb/hr
Seizure Treatment

IV Phenobarbital (65 mg/ml)

- 1-3 mg/lb IV bolus
  - Up to 15-20 minutes for full effect
  - Usually causes ataxia
- CRI if bolus not effective
  - 2-4 mg/kg/hr in D5W or 0.9% NaCl
  - Monitor for cardiopulmonary depression

Seizure Treatment

Propofol (10 mg/ml)

- 1-2 mg/kg (1-2cc per 20 lbs) IV bolus
  - Intubate if needed
  - Assist ventilation if apneic
- Anti-seizure CRI if bolus not effective
  - 0.1-0.6 mg/kg/hr in D5W or 0.9% NaCl
- Anesthesia CRI if above not effective
  - Up to 6 mg/kg IV (<3 cc per 10 lb) to effect
  - The CRI 6 mg/kg/hr
  - Monitor for cardiopulmonary depression

Seizure Treatment

Pentobarbital (50 mg/ml)

- 2-15 mg/kg (3.3 cc per 10 lbs) IV bolus
  - Give slowly over several minutes to effect
  - Intubate
- CRI if bolus not effective
  - 0.5-4 mg/kg/hr in D5W or 0.9% NaCl
  - Monitor carefully for cardiopulmonary depression
  - Dysphoria and paddling is common
  - Difficult to distinguish form seizure

Emergency Seizure Protocol

1. Stop the Seizure
   - Up to 3 diazepam boluses
     - This will last up to 30 minutes
   - If no effect, phenobarbital bolus
   - If no effect, propofol low dose bolus
   - If no effect, induce anesthesia
     - Isoflurane
     - Propofol CRI
     - Pentobarbital bolus or CRI

2. Provide Supportive Care
   - oxygen
     - By face mask if conscious
     - By tube if intubated
   - IV fluids – place catheter
     - 1 ml/lb per hour for maintenance
     - Less if CHF
     - More if dehydrated or shocky
   - Monitor temperature
     - Cool if needed
     - Warm with time (anticonvulsant therapy can drop temp)
3. Initiate Diagnostics
   - Draw blood
     - PCV/total solids
     - Check for lipemia – TG/chol
     - Glucose, calcium
     - If already taking bromide or phenobarbital, drug levels
       - prior to emergency phenobarbital administration if possible
   - Get pre-fluid therapy urinalysis

4. Prevent further seizures
   - Start PO phenobarbital 1-3 mg/lb
     - if not already given as a bolus
     - If conscious enough to swallow
     - Can give IM if can’t swallow
     - If on anticonvulsants, consider starting new drug
     - Bromide can be given rectally if can’t swallow
     - May cause transient diarrhea

5. Treat further seizures
   - More boluses if sufficient time has passed
     Anticonvulsant CRI if recent boluses ineffective
     - Diazepam CRI first
     - Then add phenobarbital or low-dose propofol
     - If still ineffective, consider anesthetic induction
     - Propofol induction
       - Maintain on isoflurane or propofol CRI
     - Or pentobarbital induction
       - Series of boluses or CRI

6. Monitor and recover
   - temperature
   - Pulse oximetry
   - Respiratory and heart rate
   - Turn every 4 hours if under anesthesia
   - Express bladder as needed or catheterize with collection system
   - If seizures recur on recovery, repeat the process
   - Some patients need to be sedated for 24-48 hours
   - Tremors on recovery from propofol anesthesia can be confused with seizures