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“Seizures! From Emergency to Maintenance”

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RECOGNITION AND DIAGNOSIS OF SEIZURES

Generalised seizures (where there is impairment of consciousness) are the most common type of epileptic seizure in dogs, while partial seizures are more common in cats. The accurate description of generalised seizures is important: 1) in order to differentiate them from other causes of collapse (e.g. syncope), and 2) because the presence of generalised seizures is one of the criteria for making a diagnosis of idiopathic epilepsy.

CLASSIFICATION OF SEIZURES BY ANATOMICAL LOCALISATION OF THE UNDERLYING CAUSE

Once we are confident that the episodes are seizure episodes the next stage is to perform the neurological examination. Epileptic seizures imply a forebrain disorder. Their causes may originate outside (extra-cranial, with symmetrical neurological deficits if present) or inside (intra-cranial) the brain. Intra-cranial causes may be further subdivided into functional disorders (no gross structural changes are evident in the brain and therefore usually no neurological deficits) and structural disorders (there is a gross structural cause within the brain, e.g. a brain tumour and often have asymmetrical neurological deficits). The most common cause of seizures is idiopathic epilepsy.
However, it is essential to recognise that seizure may cause temporary, mild neurological deficits themselves, irrespective of the underlying cause, so called “post-ictal depression”. These are usually temporary and resolve after a few hours. If you perform the neurological examination shortly after an epileptic seizure and find deficits, then repeat the assessment a day later to confirm whether they are genuine.

IDIOPATHIC EPILEPSY AS A CAUSE OF SEIZURES

Idiopathic epilepsy is the most important cause of seizures in dogs and an important cause in cats. The diagnosis of idiopathic epilepsy is a diagnosis of exclusion as there is currently no definitive diagnostic test.

Although idiopathic epilepsy is a diagnosis of exclusion there are certain clinical characteristics in dogs that make it more likely:

- Most affected dogs have their first seizure between 1 and 3 years of age, but the accepted range with a high likelihood is between 6 months to 6 years of age.
- The seizures tend to be generalised tonic-clonic seizures or partial seizures with rapid secondary generalisation (usually characterised by autonomic signs of hypersalivation and in many cases urination).
- The seizures tend to occur while the dogs are relaxed in the house or from sleep.
- There are no abnormalities in the inter-ictal period.
- There is no evidence of haematological or biochemical abnormalities.
- Certain breeds are over-represented, including: collies (in particular Border collies), Labrador retrievers, golden retrievers, Irish setters and German shepherd dogs.

95% of dogs with a seizure onset between 6 months and 6 years of age, a normal physical and neurological examination, normal blood work and with generalised seizures will have idiopathic epilepsy.

MAINTENANCE THERAPY FOR CANINE SEIZURES

The aim of any anti-epileptic treatment is to “control” the seizures by reducing their frequency, intensity and severity with minimum side effects – treatment is unlikely to totally abolish the seizures. The treatment of choice in dogs is phenobarbital or in countries where it has been launched as a veterinary prescription only medication: imepitoin (Pexion™). Individual doses of phenobarbital are determined by serum concentrations and not oral dose – the aim is to keep the blood levels within the “therapeutic range”. Imepitoin does not require monitoring of serum concentrations. In dogs with hepatic impairment then
imepitoin or potassium bromide may be used as sole maintenance therapy in dogs (but not in cats), although imepitoin is not completely hepatic safe and in severe hepatic disease levetiracetam (Keppra™), a human antiepileptic medication may be safer.

Guidelines when to start treatment:
1. Where more than one relatively brief generalised seizure occurs every two to four months and/or the owners objects to their frequency.
2. If the animal has a very severe seizure or a cluster of seizures, irrespective of the frequency of the seizures or seizure clusters.
3. The seizures are increasing in frequency or severity.
4. An underlying progressive disorder has been identified as the cause of the seizures.
5. Post-ictal signs are objectionable (e.g. aggression).

When do I get the dog back after starting imepitoin (Pexion™) therapy?
- Monitoring of serum concentrations is not required. Recheck the dog in 2 weeks to discuss the seizure control. If inadequate then increase the imepitoin dose.

When do I get the dog back after I have started phenobarbital therapy?
- Only 40% of dogs started on manufacturer’s recommended doses of phenobarbital will achieve therapeutic levels at the time of first monitoring. It is therefore essential to get the dogs back after two weeks to check the phenobarbital serum concentrations.
- The required dose to achieve therapeutic levels is even higher in dogs with lower bodyweight (and therefore higher metabolic function).
- The therapeutic range is 15 to 45 mg/l (preferably below 30 mg/l to avoid hepatic toxicity) or 65 to 174 μmol/l, depending of the units used.
TREATMENT OF EPILEPSY REFRACTORY TO PHENOBARBITAL OR IMEPITOIN THERAPY (ADJUNCTIVE THERAPY)

Refractory epilepsy is where the animal’s quality of life is compromised by frequent or severe seizures episodes, despite appropriate therapy with the first choice anticonvulsant medication. Combination therapy with phenobarbital and imepitoin is the first choice therapy in these cases. If that is not effective then potassium bromide is the next choice, at 20 to 40 mg/kg/day. Potassium bromide is not appropriate for use in cats, as around 50% will develop eosinophilic bronchoalveolitis. The response to subsequent medications in dogs that have been demonstrated to be refractory to three previous anticonvulsant medications is very poor.

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). **Loading doses of potassium bromide are not routinely used as they often result in profound sedation and ataxia.** The loading dose is 200 mg/kg daily for 5 days, after which the dose is decreased to the maintenance dose of 20 to 40 mg/kg daily. If the seizures resolve before the 5-day loading has been completed, then it is advisable to change to the maintenance level sooner, hopefully avoiding the development of marked sedation and ataxia.

Although the response to further medications is likely to be very poor, the following drugs can be considered:
- Levetiracetam (Keppra®)
- Zonisamide (Zonegran®)
- Gabapentin (Neurontin®)

PULSE THERAPY IN DOGS WITH CLUSTER SEIZURES

A cluster of seizures is defined as more than one distinct seizure episode in 24-hours. Some dogs demonstrating cluster seizures will have numerous seizure episodes in 24 to 72 hours (often as high as 18 to 20 per day), but a relatively long period between clusters (weeks). In these dogs demonstrating clusters of seizure then short term introduction of an additional drug for the duration of the cluster may be of benefit in order to reduce the number of seizures during the cluster. The drug is used in addition to the maintenance therapy and is started at the start of the cluster and stopped 2 to 3 days later. The drug is then repeated at the next cluster. The medications that I prefer and which appear to give good results in most cases with minimal side effects are imepitoin at 30 mg/kg BID to QID (off label) or levetiracetam at 30 to 40 mg/kg QID
for the duration of the cluster (usually for 2 to 3 days) and then stopped again until the start of the next cluster.

**TREATMENT OF SEIZURES IN CATS**

Although idiopathic epilepsy in cats is an important cause of seizures, other systemic and/or neurological findings are common – it is therefore important to assess for the presence of underlying causes in cats. Treatment of seizures in cats relies on phenobarbital, diazepam or levetiracetam as maintenance drugs of choice. Phenobarbital does not result in enzyme induction and the elimination half-life therefore remains stable in cats. Potassium bromide should not be used in cats due to unacceptable side effects and imepitoin has not been safety tested in cats.

**EMERGENCY MANAGEMENT OF SEIZURES**

The emergency management of seizure involves the simultaneous instigation of: 1) Control of the current seizures with short-acting anti-convulsant medications, 2) Controlling deleterious systemic effects: in particular hyperthermia, 3) Ensuring adequate blood levels of a maintenance anti-convulsant medication (usually imepitoin or phenobarbital) so that there is an effective anti-convulsant medication on board for when the emergency short-acting drugs wear off, and 4) Sample collection for diagnostic evaluation: particularly to exclude metabolic causes of seizures (e.g. hepatic encephalopathy or hypoglycaemia).

Status epilepticus can be defined as continuous seizure activity lasting longer than 30 minutes or two or more seizures without full recovery of consciousness during the inter-ictal period. However immediate treatment is required in any prolonged seizure.

1. **CONTROL OF THE CURRENT SEIZURES WITH SHORT-ACTING ANTI-CONVULSANT MEDICATIONS:**

   - **DIAZEPAM IS THE DRUG OF CHOICE FOR STATUS EPILEPTICUS**
     
     Bolus dose of 0.5 to 1 mg/kg intravenously. Time to onset of clinical effect is 2 to 3 minutes for intravenous administration, therefore repeat if there is no clinical effect up to three times. If venous access is not available then the diazepam can be administered rectally: in this case a higher dose is used for emergency seizure control under veterinary supervision of 1 to 2 mg/kg rectally. The time to onset of clinical effect is longer for the rectal route. The elimination half-life is longer in cats and care must therefore be taken to avoid overdosing.

   - Midazolam: is an alternative to diazepam, or can be used in conjunction with diazepam. It is used at a bolus of 0.2 mg/kg IV and then can be continued as a constant infusion at a starting dose of 0.3 mg/kg/hour in saline.
2. CONTROLLING DELETERIOUS SYSTEMIC EFFECTS:
When the dog or cat presents in status epilepticus consideration must be given to the following factors as a priority:

- Establish intravenous access.
- Maintain normal body temperature as status epilepticus may result in hyperthermia and this is an important cause of mortality in dog following status epilepticus. All cooling method should be stopped when rectal temperature reaches 102°F or 39°C as over-shoot hypothermia may occur – particularly as diazepam impairs normal thermoregulation. The ideal method of cooling is ice packs wrapped in wet towels placed on the large blood vessels: axilla and groin. These ice packs can then rapidly be removed when the body temperature approaches normal.
- If required: maintain patent airway and administer oxygen by face mask.
- Administer IV NaCl 0.9% with KCl 26 mEq/L at maintenance rate (Lactate Ringer may result in microprecipitation of intravenous diazepam or midazolam).

3. ENSURING ADEQUATE BLOOD LEVELS OF A MAINTENANCE ANTI-CONVULSANT MEDICATION
The choice of maintenance anticonvulsant will depend on whether the dog has been on treatment for seizures before and if so which one. Imepitoin will give immediate therapeutic serum concentrations after the first dose, while phenobarbital will require a loading dose to achieve therapeutic levels.

- If the dog has not been on maintenance anticonvulsant therapy when it went into status epilepticus: Start either imepitoin at 30 mg/kg BID or a loading dose of phenobarbital (followed by maintenance doses thereafter). If loading phenobarbital then give an initial dose of 12 mg/kg. After 20 minutes give a further bolus of 4 to 6 mg/kg, repeat this bolus of 4 to 6 mg/kg again after a further 20 minutes to take the total dose to 18 to 24 mg/kg. CNS levels, and therefore clinical effect, takes 20 minutes to achieve, therefore wait 20 minutes before injecting more phenobarbital after each bolus to ensure that the dog does not become excessively sedated. Always return to the maintenance dose of 2 to 3 mg/kg BID once the loading is completed.
- If the dog was on imepitoin when it went into status epilepticus then increase the dose of imepitoin to 30 mg/kg BID and start a loading dose of phenobarbital.
- If the dog was on maintenance phenobarbital therapy when it went into status epilepticus then give a single bolus of 4 to 6 mg/kg IV or IM to slightly increase the serum phenobarbital concentrations in case they were sub-therapeutic and start imepitoin.
• You can also consider starting a loading dose of potassium bromide, while controlling the dog in the short term with levetiracetam, if the phenobarbital or imepitoin is not effecting in an individual patient.

4. SAMPLE COLLECTION FOR DIAGNOSTIC EVALUATION:
Particularly to exclude metabolic causes of seizures (e.g. hepatic encephalopathy or hypoglycaemia).

FOLLOW-UP:
Seizures stop:
All patients should receive maintenance doses of anticonvulsants.

Seizures continue:
If seizures are continuing at a lower frequency, administer additional intravenous bolus doses of Diazepam at 0.5 mg/kg. If seizures continued at high frequency then the affected animal should be sedated or anaesthetised with a suitable anti-convulsant medication for 12 to 36 hours and then recovered.
• Administer continuous Diazepam infusion at an initial rate of 1 mg/kg/hour in dogs and 0.5 mg/kg in cats. Care should be taken in cats to avoid overdosing. OR
• Continuous Midazolam infusion: Sedate the animal with a bolus of 0.2 mg/kg IV and then continue as a constant infusion at 0.3 mg/kg/hour in saline (not in Hartman’s due to precipitation with the calcium). Further boluses can be given to effect on top of the infusion. Midazolam continuous infusions have the advantage that the animal is sedated, but still able to eat and go to the toilet with support. OR
• Continuous Levetiracetam (Keppra) infusion. OR
• Continuous Propofol infusion at 1-3 mg/kg/hour or to effect. OR
• Inhalation anaesthesia as a last resort.