In fits and starts – managing canine epilepsy: part one

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Kerry Hall BSc(Hons), DipAVN (Surgical), discusses epilepsy management, with particular focus on seizure types and medication choices

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THE two articles in this series will discuss the management of canine seizure patients, both in long-term and emergency situations. The aim is to increase VN knowledge and, therefore, confidence to deal with what can be challenging cases.

This article assumes a diagnosis of primary or idiopathic epilepsy has been reached after a thorough clinical workup – including full haematology and biochemistry profiles and bile acid stimulation testing – and serology for infectious disease agents and advanced brain imaging (such as magnetic resonance imaging and cerebrospinal fluid analysis) if possible. However, it must be remembered that dogs may seizure for many reasons (metabolic or toxic causes), and the diagnosis should constantly be re-evaluated.

Definitions

Seizure. In this article, the term seizure is specifically used to refer to an epileptic seizure – a clinical manifestation of abnormal electrical activity in the brain. It is a specific event in time.

Epilepsy. Multiple seizures occurring over a long period of time.

Idiopathic epilepsy. This implies that no underlying structural brain lesion or reactive cause is present, and is presumed to be genetic in origin.

Refractory epilepsy. No improvement in seizure frequency, number and severity, despite therapeutic serum levels of phenobarbital and/or potassium bromide (KBr).

Cluster seizures. Two or more seizures in a 24-hour period.

Status epilepticus. A continuous seizure lasting at least five minutes, or two or more discrete seizures, between which the patient does not fully recover consciousness.

Seizure descriptions and classifications

It is useful for VNs to be able to accurately describe the episode witnessed. The three seizure "types" are:

• self-limiting (isolated);

• clustered (two or more seizures in a 24-hour period); and

• status epilepticus (SE).

Within each category, the seizure can be further subdivided into focal or generalised.

Clinical features of epileptic seizures include:

• prodrome – the time period before onset of seizure activity (owners report that they can sometimes predict their pet's seizure by behaviour changes such as restlessness or anxiety);

• aura – the initial manifestation of a seizure (this period can last from minutes to hours when animals exhibit sensory or motor behaviour, such as pacing or licking, or autonomic behaviour such as salivation, urination or vomiting. Owners also report that their animals are more agitated, hiding, or seeking the owner);

• ictal period – this is the actual seizure event (this usually lasts seconds to minutes); and

• post-ictal period – this is the period after the seizure, which can last minutes to days. Unusual behaviour – such as disorientation, confusion, blindness and ataxia – may be observed.

Owner expectations

Before the start of any treatment, the owner must be fully informed of the financial and emotional

costs of caring for an epileptic pet. Usually, this is discussed by the veterinarian, but when consultation time is restricted and the client “doesn’t like to trouble the vet”, this often means questions are left unanswered, which is where the VN’s role is vital.

Key points

Owners must appreciate the importance of administering medication at the prescribed dose and interval. They must understand that no changes should be made to the medication regime, unless under the direction of a veterinary surgeon.

Owners must ensure they keep a supply of medication at home to avoid running out. Suddenly stopping anti-epileptic medications may precipitate seizures and should, therefore, be avoided at all costs. The importance of keeping all appointments at the clinic must be stressed to owners, whether it is for repeat prescription checks or regular serum monitoring tests.

Owners should be aware of what to do in the case of further seizures, and be prepared to administer rectal diazepam as directed by the veterinary surgeon, and seek emergency advice or a consultation as necessary. It is also important they are made aware of the possibility of status epilepticus and that, if this develops, the consequences may be life threatening for their pet. For this reason, timing the seizure activity is highly recommended.

It is advised that owners keep a seizure diary for their pet. The information recorded should include date, time and a detailed description of what the pet does before, during and after a seizure. The duration of the seizure itself should be timed with a watch. In addition, information regarding possible triggers can be recorded to allow any trends to be noted – for example, do they happen at a certain time of day?

Behaviour in the inter-ictal periods may help to identify pre-ictal signs to act as a predictor of seizure activity.

Medications can be recorded (name, dosage and time of administration), with any drug side effects noted. The diary can then be taken along to any consultation to assist the veterinarian in tailoring a treatment protocol to meet the animal’s individual needs.

Owners must be realistic in their expectations. Their pet will not be cured with medication, but instead managed to allow for a quality life (for both owner and pet). The ideal outcome would be to completely stop any seizure activity without any drug side effects, but this is unrealistic. The owner must appreciate it is very likely the animal will still seizure, despite medical management. Treatment is deemed successful if seizures are reduced by more than 50 per cent. Owners also need to be aware that patience is required. It takes time for anti-seizure medication to reach therapeutic levels, and they must not discontinue therapy prematurely. If the animal has not been neutered, this should be recommended to the owners to avoid breeding, due to the potential for

epilepsy to be inherited.

Many owners will seek further information online and, while a lot of information is available, much of it is not peerreviewed. It should be recommended that only information written by a specialist in veterinary neurology be considered and owners should preferably discuss it with their own vet before making any changes to their pet's lifestyle.

A good website to recommend in the first instance may be www.canineepilepsy.co.uk

Telephone advice

When clients encounter a seizuring animal, their first point of contact with a practice is often by telephone. If it is their first experience of a seizure, they will be very upset and distressed by the situation. As VNs taking these calls, we must be confident in what we are advising the client and, at the very least, avoid putting the client on hold.

Key points

• Be clear and concise when giving instructions, as the clients are relying on us to do our best to calm the situation.

• Advise clients to move out of the way anything that may cause further injury to their pet.

• The client should remove any stimuli, such as noise and light.

• They should not try to restrain their pet, as it is likely they will get bitten due to the animal being unaware of its surroundings.

• Advise that the voidance of urine and faeces, and increased salivation, during a seizure are a normal occurrence.

• Ideally, the seizure length should be timed, as owners will often perceive the duration to be longer (if it's your pet seizuring before you, it will often seem like a lifetime), rather than the few minutes each seizure actually lasts.

• Owners should be advised to handle their pet carefully in the post-ictal stage, as it is likely to be confused, disorientated, potentially aggressive and may be blind for hours or sometimes days following severe and prolonged seizure activity.

• Clients should be advised to seek a veterinary consultation as soon as possible. The vet will perform a thorough clinical and neurological examination and begin the necessary investigations, which may involve referral to a neurology specialist.

When to start treatment

The decision on when to initiate treatment will be made by the veterinary surgeon in charge of the case (in consultation with the owner), but VNs should also be informed as to when treatment is likely to be initiated.

Anti-epileptic treatment should be started in dogs with idiopathic epilepsy that have:

• more than one generalised seizure per month;

• status epilepticus or severe cluster seizures;

• severe, unusual post-ictal events (aggression and blindness);

• the seizures are increasing in frequency or severity; and

• in addition, anti-epileptic treatment should be started in dogs with seizures secondary to structural brain disease, such as cerebral neoplasia or infection/ inflammation and when the first seizure occurs within one week of head trauma.

Anti-epileptic medications

Maintenance therapy

Generally speaking, phenobarbital and KBr are the medications of choice because they are:

• licensed for canine use;

• relatively safe;

• effective;

• relatively inexpensive; and

• are a familiar drug seen in veterinary practice.

Therefore, it is these two drugs that I will focus on, but I will also mention newer (unlicensed) medications that may, in certain situations, be appropriate.

Some patients do well on monotherapy, whereas others do better with polytherapies. It is very important that the first medication, generally phenobarbital, is used correctly – for example, a medium or high therapeutic level is reached and maintained for enough time before a second

medication is introduced.

Phenobarbital

In my experience, phenobarbital is the mainstay treatment option in canine epileptic patients. It is effective in 60 to 80 per cent of dogs with idiopathic epilepsy if serum concentrations are maintained within the target range (Thomas, 2010). Phenobarbital is available in either a tablet or liquid formulation, which allows for accurate dosing.

The initial dose is 2.5mg/ kg to 3mg/kg bid, and subsequent dosing is guided by serum levels. Ideally, once a patient has been started on phenobarbital, the serum levels should be checked after two weeks (a steady state being achieved in 10 to 15 days in the canine patient). Therapeutic levels of phenobarbital should be between 15mg/L and 45mg/L (ideally less than 35mg/L to avoid hepatotoxicity), aiming initially for a serum level between 20mg/L and 30mg/L. If the serum concentration is below the therapeutic range, the dose should be increased (increasing the dose by 10 to 30 per cent is suggested).

If the serum concentration is above the therapeutic range, the risk of hepatotoxicity is increased and the dose should be decreased. Serum phenobarbital levels should be checked:

• two weeks after the start of treatment or any change in dose;

• if the patient’s seizure frequency increases;

• once the phenobarbital therapeutic level has been achieved and seizure control is satisfactory; and

• every six to 12 months to ensure serum concentrations remain within the therapeutic range.

Phenobarbital will induce cytochrome P450, a liver enzyme that results in an increased rate of metabolism of the medication. This means that the serum levels may fall despite a constant oral dose, and seizure activity may worsen.

Owner commitment

Obviously the above is the ideal, but it must be appreciated that owners may be reluctant to start treatment, usually for financial reasons. However, if they are made fully aware of commitments from the outset, this should be less of a problem.

The blood sample drawn should be a fasted sample in a serum tube. Serum gel tubes should be avoided, as phenobarbital can bind to the gel, resulting in falsely low readings. The timing of the sample in relation to time of drug administration is less important, especially at doses less than

4mg/kg bid.

However, if concern over the efficacy of seizure control exists, both peak (four to six hours post-medication) and trough (immediately prior to the next dose of medication) samples should be obtained.

Side effects of phenobarbital

It is important for the VN to be aware of the side effects of this commonly used drug so they know what to look for in the hospitalised patient and are able to give advice to owners. Side effects can occur but they are often dose-dependent and the effects are usually transient, lasting one to three weeks.

Short-term side effects may include:

• sedation and ataxia;

• hyperexcitability and restlessness; and

• polydipsia and polyphagia.

Long-term side effects may include:

• haematological abnormalities, such as neutropenia, anaemia and thrombocytopenia;

• hepatotoxicity is rare, but can be seen at higher serum concentrations (more than 35mg/L); and

• clinical signs of hepatotoxicity include anorexia, sedation, ataxia, icterus and ascites.

In some cases, “loading” doses of phenobarbital may be indicated and doses of up to 18mg/kg/day administered. Dosing at these levels will be associated with the increased likelihood of sedation, ataxia, polyuria and polydipsia being observed, as there is no time to build up tolerance compared to gradual increases. Preferably, the total dose should be divided, with the administration spaced out over 24 hours to minimise the risk of profound sedation.

Potassium bromide

KBr can be used as a sole agent where phenobarbital use is contraindicated, or as an add-on treatment for patients already on phenobarbital.

If used as a monotherapy dose (20mg/kg bid or 35mg/kg sid) or if being used as an add-on to phenobarbital where phenobarbital serum levels are 25mg/L to 35mg/L and seizure control is

unsatisfactory, a dose of 20mg/kg to 30mg/kg sid is recommended. Ideally, KBr should be provided with food, as it can cause gastric irritation.

KBr can take up to four months to reach a steady state, after which serum levels can be monitored (therapeutic levels are between 2mg/ml and 3mg/ml if monotherapy, or between 1mg/ml and 2mg/ml if used as an add-on treatment).

Side effects of KBr may include:

• sedation;

• weakness;

• pelvic limb ataxia;

• vomiting and diarrhoea (due to gastric irritation by the hypertonic bromide salts);

• polyuria, polydipsia or polyphagia;

• pancreatitis;

• erythematous dermatitis; and

• hyperactivity.

As with phenobarbital treatment, KBr loading may be more appropriate for those patients you want to reach therapeutic serum concentrations sooner – for example, if you need to withdraw treatment with phenobarbital or despite phenobarbital treatment, seizure activity is increased. The loading dose is 100mg/kg/day (25mg/kg every six hours to minimise the sedative effects and gastric irritation) for five days, before returning to a maintenance dose at day six. Serum levels should be checked after one week.

It is recommended that the patient be hospitalised if undergoing KBr loading, due to the side effects of sedation and ataxia. These can be quite marked, and the patient may require support when exercising. Due to gastric irritation, vomiting and diarrhoea can also occur.

KBr is mainly excreted by the kidneys, where it competes with chloride for excretion. Increased chloride intake results in increased bromide elimination, which increases the dose requirement. It is very important that diets high in salt be avoided, along with any sudden change in sodium chloride intake, such as consumption of salt water (on trips to the seaside), crisps or sausages during parties or barbecues.

Another key point of clinical importance is that, where possible, patients on KBr therapy should not be placed on saline (sodium chloride) intravenous fluids, as this will result in the “washing out” of bromide, and it is likely that the patient will start seizuring again. Conversely, sudden decreases in salt intake may result in an increase in sedation and other bromide side effects.

Bromism is the term given to bromide toxicity. Signs of bromism include:

• stupor or coma;

• blindness;

• ataxia;

• paraparesis;

• tetraparesis;

• dysphagia; and

• megaoesophagus. In this case, the bromide dose should be decreased or withdrawn.

Newer medications (unlicensed)

Examples of newer anti-epileptic medications include the following unlicensed products.

Levetiracetam. This is considered an effective drug in humans with minimal side effects. The majority (70 to 90 per cent) is excreted unchanged in the urine – care should be exercised in canine patients with renal insufficiency.

The fact it is not metabolised by the liver may make it a useful alternative or add-on medication in patients with hepatotoxicity or seizure activity secondary to liver disease or portosystemic shunt. The dose rate is 20mg/kg tid. It also comes in an injectable form, which may make it a good choice for the loading of patients in status epilepticus that are refractory to other, licensed drugs, or have liver disease.

Gabapentin. While its mode of action is not fully understood, gabapentin is believed to block seizures induced by a variety of proconvulsant methods. The drug is renally excreted, which may make it beneficial in patients with underlying hepatic disease. Therefore, doses may need to be reduced in patients with renal insufficiency. Studies have shown gabapentin is best used as an add-on therapy, rather than a monotherapy medication. Side effects may include excessive sedation and ataxia. The dose rate is 10mg/kg to 20mg/kg orally tid, although patients should always be started at the lower dose rate due to the sedation risk.

Zonisamide. This is considered to be a well-tolerated drug. It has been shown that adding zonisamide improves seizure control in 80 to 90 per cent of dogs whose seizures are poorly controlled by other drugs. It may be a good choice for initial therapy to minimise side effects seen with other drugs. If used as monotherapy, the initial dose is 5mg/kg orally bid. If used in combination with phenobarbital, the dose is 10mg/kg due to increased excretion. Licensed zonisamide products for dogs are not available, and treatment for veterinary patients is often cost-prohibitive in the UK.

• **Part two of this article will discuss the emergency management of seizuring patients.**

Reference

- Thomas W B (2010). Idiopathic epilepsy in dogs and cats, *Vet Clin of North Am (Small Anim Prac)* **40**: 161-179.