Treatment and monitoring of epilepsy in dogs

Kate Chandler

Epilepsy is a brain disorder and is defined as the propensity to have recurrent seizures. It is the most common chronic neurological disorder seen in dogs. Most dogs that present with recurrent seizures have idiopathic epilepsy, which is thought to have a genetic basis and has no identifiable underlying cause when a full diagnostic work-up is undertaken. Symptomatic epilepsies, which arise secondary to brain diseases such as intracranial neoplastic lesions or central nervous system inflammatory disorders, are less common. By addressing some of the most frequently asked questions relating to the treatment of seizures, this article suggests some practical and effective strategies for managing and monitoring dogs with idiopathic epilepsy.

Types of seizure

Seizures may be focal or generalised. Focal seizures arise when only part of one cerebral hemisphere develops abnormal epileptiform activity, while generalised seizures arise when there is significant abnormal activation of both cerebral hemispheres. There are several different types of focal and generalised seizure (Chandler 2006). Typically, generalised seizures have tonic and clonic components (periods of rigidity and rhythmic movements, respectively), are symmetrical and involve most of the body. Focal seizures are often asymmetrical and may appear as limited movements of isolated parts of the body, such as lip twitching or rhythmic movements of a limb.

Should treatment be initiated?

The key point when considering initiating treatment for epilepsy is to think about the effect that the seizures have on the:

- Quality of life;
- Brain.

If the seizures are occasional and there is no evidence of increasing frequency or severity, treatment may not be necessary (see Table 1). There is much debate in the literature about whether ‘seizures beget seizures’. From human clinical evidence, it is thought that treating the first seizures that occur at the onset of epilepsy does not actually change the progression of the condition. It is therefore unlikely that leaving seizures untreated affects the progression of epilepsy, unless a patient has clusters of seizures or has had a period of status epilepticus (see below).

A cluster of seizures is defined as more than one seizure event in 24 hours. Animals that have clusters of seizures are at risk of going into status epilepticus, so antiepileptic drug treatment should be instituted immediately in such patients.

Status epilepticus is defined as prolonged seizure activity lasting longer than five minutes. It affects neurons and circuitry within the brain, which predisposes

<table>
<thead>
<tr>
<th>Table 1: Management of recurrent seizures</th>
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<tr>
<td>Reasons to treat</td>
<td>Reasons not to treat</td>
</tr>
<tr>
<td>Animals have one seizure or more per month Quality of life is decreased by the seizures, or by the prodromal or postictal periods There is a history of clusters of seizures or status epilepticus Seizures increase in frequency or severity</td>
<td>Seizures do not appear to be affecting an animal’s quality of life Seizures are infrequent (eg, less than one per month) Seizures are very brief and ‘mild’ (eg, focal seizures) The side effects of the antiepileptic drugs are likely to affect quality of life more than the seizures themselves</td>
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</table>
it to further seizure activity. Hence, any epileptic dog that has a period of status epilepticus should be treated with antiepileptic drugs.

Owner communication is a key part of managing epileptic dogs. It is vital that owners understand that antiepileptic drugs control seizures but do not cure epilepsy. It is also important to be aware of owners’ wishes, and to consider how any treatment and monitoring regimen will fit into their lifestyle. Many owners have difficulty in understanding that therapy may not lead to a seizure-free patient, and may still request treatment even if the seizures are very infrequent. If, for example, seizures occur every three months, giving twice daily treatment that may cause side effects is usually not appropriate.

Occasionally, owners will decline treatment against the veterinary surgeon’s advice. This often occurs if clients have researched antiepileptic drugs on the internet and have learned that drugs such as phenobarbital have a significant risk of causing side effects and toxicity. In addition, some owners will be unable to give twice daily treatment because of their lifestyle. Providing there are no signs to suggest that an animal is at risk of going into status epilepticus, leaving an epileptic dog untreated may be acceptable. In such situations, it is important to be confident that the animal’s quality of life is not affected by the seizures, and particularly that the prodromal and postictal periods are brief and associated with no or only mild behavioural change. Owners need to monitor seizure duration and severity, and the interictal period to ensure that there is no evidence of worsening. It would also be prudent for owners to keep diazepam at home, which can be administered per rectum if status epilepticus occurs.

What are the treatment options and what monitoring is required?

Phenobarbital and potassium bromide are both appropriate choices for first-line antiepileptic drugs in the dog (see Table 2). Each drug has advantages and disadvantages, and the choice is very much tailored to the individual patient. Phenobarbital needs to be administered twice daily, while potassium bromide is effective when given once daily (although it is tolerated better when the dose is split into two daily doses). Potassium bromide can be difficult to manage if dose changes are made frequently due to its long half-life. Each time the dose is changed, it takes at least three months to reach a steady state. Potassium bromide is more likely to cause vomiting but phenobarbital is hepatotoxic in some patients, particularly following the long-term use of high doses.

Phenobarbital

One of the most common mistakes when using phenobarbital is to start on an inappropriately low dose and to stop treatment abruptly when it has not been effective (see Box 1). A dose of 3 mg/kg twice daily is sufficient to achieve a therapeutic serum concentration in the majority of dogs. It takes seven to 14 days to reach a steady state because the elimination half-life is approximately 40 to 90 hours. This means that the drug may not start to be effective until that point, and any side effects are more likely to be obvious during this period. However, after the first 14 days, side effects often begin to improve.

When using phenobarbital, owners should be informed about:

- Its potential side effects, which include:
  - Sedation, polyuria, polydipsia and polyphagia;
  - Ataxia and paresis;
  - Hyperexcitability and aggression;
  - Neutropenia, lymphopenia and anaemia (bone marrow necrosis is uncommon);
  - Necrolytic dermatitis (this is uncommon and does not usually resolve if treatment is ceased);
  - Hepatotoxicity (see Box 2);
- Metabolic tolerance (hepatic microsomal enzyme induction). When this occurs, the body increases its ability to metabolise the drug over time, which can lead to gradual or sudden increase in seizure frequency in dogs that are on an unchanged dose of phenobarbital, and the dose may need to be increased to keep the same level of seizure control;
- The need for life-long treatment;
- The need for 12-hour dosing;
- The importance of not stopping therapy. A sudden withdrawal of phenobarbital may cause status epilepticus.

Serum concentrations should be checked seven to 14 days after starting therapy or changing the dose. In

### Table 2: Treatment options for epilepsy in dogs

<table>
<thead>
<tr>
<th>Drug</th>
<th>First-line or add-on drug?</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>First-line or add-on</td>
<td>3 mg/kg twice daily</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td>First-line or add-on</td>
<td>15 mg/kg twice daily as an add-on drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or 20 mg/kg twice daily as a first-line drug</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Add-on</td>
<td>10 to 20 mg/kg three or four times daily</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Add-on</td>
<td>10 mg/kg three times daily</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Add-on</td>
<td>10 mg/kg twice daily</td>
</tr>
</tbody>
</table>

Box 1: Common mistakes when using phenobarbital

- Not giving a high enough dose. A starting dose of 3 mg/kg twice daily is sufficient and appropriate for most dogs
- Not increasing the dose when the serum concentration is at the low end of the therapeutic range (eg, assuming that 15 μg/ml will be effective when, in fact, many dogs need a higher serum concentration)
- Poor owner compliance/incorrect dosing interval
- Not monitoring serum concentrations
- Abrupt withdrawal of the drug, leading to status epilepticus or more severe seizures
- Giving extra daily doses if a seizure is expected (there is no evidence that this is useful)

Box 2: Liver function tests

Dogs on long-term phenobarbital treatment, particularly if serum concentrations are consistently above 35 μg/ml, are at risk of hepatic failure. However, elevation of liver enzymes, particularly alkaline phosphatase, is quite usual in dogs on phenobarbital and is not necessarily a sign of liver dysfunction. It is therefore not useful to use liver enzymes in isolation as a test for hepatotoxicity. Instead, measuring pre- and postprandial bile acids every six to 12 months, or more frequently if liver dysfunction is specifically suspected in a patient, is appropriate.

It should also be noted that phenobarbital decreases thyroxine and free thyroxine, and increases thyroid-stimulating hormone (Gaskill and others 2000). However, this is not associated with clinical signs of hypothyroidism and thyroid supplementation is not indicated.
addition, they should be measured every three to six months as a matter of routine, if seizures are poorly controlled or if side effects increase. The therapeutic range is 15 to 45 μg/ml. However, many epileptic dogs will not respond until the serum concentration reaches at least 25 μg/ml. It is thought that there is a greater risk of hepatotoxicity at serum concentrations of more than 35 μg/ml. Therefore, if 25 to 35 μg/ml is insufficient to cause acceptable seizure control, a second drug, usually potassium bromide, should be added.

The dose required for a desired serum concentration is calculated using the following formula:

\[
\text{New oral dose} = \frac{\text{Old oral dose} \times \text{Current serum concentration}}{\text{Desired serum concentration}}
\]

There has been much discussion about whether trough samples (ie, the sample taken when the serum concentration is at its lowest) are valuable when monitoring phenobarbital concentrations. In most patients, the timing of sampling does not appear to be important, as the serum concentration during steady state does not vary much during the day. However, if a patient tends to have seizures at a particular time of day, this may suggest breakthrough seizures when the serum concentration drops at a particular time each day. In such cases, a sample taken at the time of typical seizure activity could be very useful. The trough level occurs approximately two hours before the evening dose is due.

**Potassium bromide**

Potassium bromide is appropriate as a first-line antiepileptic drug in dogs, or it can be used as a second drug in dogs that have epilepsy that is refractory to phenobarbital. It should not be added until the serum concentration of phenobarbital is 25 to 35 μg/ml. The main problem associated with the use of potassium bromide is its very long elimination half-life (around 24 days). Therefore, when changing the dose in order to alter the serum concentration, it is important to remember that it can take around three to six months to reach a steady state.

Potassium bromide is a suitable choice for animals with liver disease as it is renally excreted. It should be noted that a sudden change in salt content in the diet may affect potassium bromide excretion. For example, if a high salt diet is started (eg, some prescription urinary diets), potassium bromide elimination will increase, serum concentrations may drop and breakthrough seizures may occur. Drinking excessive sea water may have a similar effect. Owners should be informed that changing the salt content of an animal’s diet may affect potassium bromide levels and seizure control.

It should be noted that although potassium bromide is well tolerated and safe in most dogs, acute pancreatitis, which is potentially fatal, is a recognised side effect in patients given a combination of phenobarbital and potassium bromide (Gaskill and Cribb 2000). In addition, there is some anecdotal evidence that potassium bromide is occasionally associated with the development of megaesophagus.

Potassium bromide may be administered at a dose of 15 mg/kg twice daily when used as an add-on with phenobarbital. Alternatively, it may be given at a rate of 20 mg/kg twice daily when used as a first-line drug. It is generally very safe to use. It should be given with food to avoid vomiting.

**Side effects include:**

- Vomiting;
- Ataxia and paresis (which can both be severe);
- Polyuria, polyphagia and polydipsia;
- Acute pancreatitis;
- Megaesophagus (anecdotal);
- Worsening of pruritus in atopic patients.

Although it takes three to six months to reach a steady stage, measuring the serum concentration at one month and three months provides information about whether the animal is on approximately the right dose. The therapeutic range is 1000 to 3000 μg/ml but, in practical terms, the dose can be increased until side effects are intolerable or there is clearly no improvement in efficacy. Timing of sampling is not important.

**When should a second or third antiepileptic drug be added?**

In patients refractory to phenobarbital and/or potassium bromide, polytherapy should generally be avoided, if possible. The serum concentration of phenobarbital and/or potassium bromide should be at the high ends of the recommended ranges before other drugs are added to make sure animals are really resistant to phenobarbital and/or potassium bromide. A third drug is often not particularly effective and owner compliance can be a major issue. Owners need to fully understand that a third drug may not have much effect. However, new human drugs are continually being developed and some are effective in epileptic dogs.

**Which add-on drug should be used?**

**Levetiracetam**

Levetiracetam, given at the recommended dose of 10 to 20 mg/kg three times daily, is arguably the most effective third-line antiepileptic drug in dogs (Volk and others 2008). It has minimal side effects, which may include sedation, but these are generally rare and mild. It needs to be given three times daily or, possibly, four times daily in some patients. It has a short half-life (approximately 3–6 hours) and therefore does not reach a steady state. However, it can significantly affect seizure frequency in cases of pharmacoresistant epilepsy. Levetiracetam is renally excreted. The main drawback of using levetiracetam is that it is usually only efficacious for around six months. In addition, it is expensive.

**Gabapentin**

Gabapentin has also been recommended as an add-on drug in dogs (Platt and others 2006). It is predominantly renally excreted, but is also partially hepatically metabolised. It can cause sedation and ataxia, but this is usually very mild. The recommended starting dose is 10 mg/kg three times daily. It has a very short half-life. Pregabalin, a closely related drug, has also showed promise in cases of epilepsy (Dewey and others 2009).
Zonisamide

Zonisamide may also be useful as a third drug (von Kloppmann and others 2007). The half-life is typically about 15 hours, but it is heptatically metabolised, so care needs to be taken when using it with phenobarbital. The recommended dose is 10 mg/kg twice daily. It may cause sedation and ataxia.

How should the issues of owner compliance, counselling and communication be handled?

Owners can find it difficult to come to terms with being told that their dog is epileptic. They often struggle with the concept that epilepsy can only be controlled and never cured. In addition, generalised seizures are violent and can be very distressing to see. Owners often fear that their dog may suffer injury or brain damage during the seizure. Therefore, they typically need regular veterinary advice and general support. The following checklist is useful when discussing epilepsy with owners to inform them of what to expect and what they need to do to aid a more satisfactory outcome:

- Single seizures lasting one to two minutes are unlikely to cause significant brain damage;
- Animals are unlikely to be aware of a seizure;
- Stopping antiepileptic drugs suddenly is dangerous, so owner compliance is imperative;
- Clusters of seizures or status epilepticus are life-threatening and veterinary assistance must be sought immediately if they occur.

Compliance among owners is generally better if they are warned in detail about the side effects of antiepileptic drugs. These should therefore be discussed with owners or a list provided for them to take home. Owners should be encouraged to keep a seizure diary, which will help them to monitor the effect of a drug objectively. It will also help the veterinary surgeon to make decisions about drug changes.

How should pharmacoresistant patients be managed?

If phenobarbital and potassium bromide administration at doses that achieve therapeutic concentrations and a steady state does not result in a decrease in seizure frequency of 50 per cent or more, the patient is deemed to have pharmacoresistant epilepsy. In humans, failure of seizure control within nine months of treatment by a neurologist is one of several definitions that are used. For these human patients, if all medical management fails, surgery is possible in some cases. This is currently not an option for most epileptic dogs and cats.

It is estimated that around a third of dogs with epilepsy do not respond well to phenobarbital and/or potassium bromide. This may be due to:

- An altered expression of drug transporters in the brain, which pump antiepileptic drugs away from where they are needed; or
- Changing drug targets in patients with recurrent seizures, which make them resistant to antiepileptic drugs.

Diagnostic and treatment errors may lead to ‘pseudo-pharmacoresistance’, and there are several questions that need to be asked if a patient is apparently pharmacoresistant:

- Has a diagnosis been made?
- Is the diagnosis correct, or is further investigation required?
- Is the treatment correct? That is, is an appropriate antiepileptic drug being used?
- Is the treatment being given appropriately? Here, consideration should be given to owner compliance issues, dosing regimens (every 12 hours not twice daily) and dietary changes that could affect drug elimination.

- Have serum concentrations been measured?
- If appropriate, have trough levels been measured?
- Has the correct serum concentration been targeted?

With phenobarbital, a serum concentration of 2.5 to 35 µg/ml (range 15 to 45 µg/ml) may be necessary for an effective response.

How should status epilepticus be treated?

The traditional definition of status epilepticus was continuous seizure activity lasting more than 30 minutes. However, more recently, the more clinically useful definition is continuous seizure activity lasting longer than five minutes.

In patients experiencing status epilepticus, the most urgent priorities are to ensure a clear airway, breathing and circulation, and to stop the seizures. Affected animals should be given intravenous or rectal diazepam at 0.5 to 1 mg/kg, and an intravenous catheter should be placed immediately. Once the patient has stopped seizing, history, physical and neurological examination needs to be performed. Other priorities include the measurement of serum glucose and electrolytes. Rectal temperature should be maintained at between 37 to 39.5°C. Finally, fluid therapy should aim to

Box 3: Loading protocols

Loading protocols should be used if serum concentrations need to be raised rapidly. This is recommended in animals that:

- Have presented following a cluster of seizures;
- Are not on antiepileptic treatment;
- Have recently been treated for status epilepticus;
- Have a very high seizure frequency.

Phenobarbital

- Step 1. Administer 3 mg/kg intravenously every 30 minutes until a total dose of up to 20 mg/kg has been given
- Step 2. Reduce the dose to 3 mg/kg intravenously every six hours for 24 hours
- Step 3. Reduce the dose to 3 mg/kg orally twice daily for continued long-term use

Note animals will be very sedated during this time and will need to be hospitalised.

Potassium bromide

- Animals can be loaded over five days, with the drug being given orally at a dose of 125 mg/kg/day orally (divided am and pm), and then 20 mg/kg twice daily or
- Animals can be loaded over one day, but this requires hospitalisation. In this case, the dose is given orally at a dose of 100 mg/kg every six hours for 24 hours. A dose should be skipped if the patient becomes obtunded.
achieve normohydration and normotension to ensure that cerebral blood flow is maintained.

Diazepam at a dose of 0.5 to 1 mg/kg should be given up to three times intravenously or rectally. If this fails to stop the seizures, it is likely that the patient is refractory to diazepam. At this stage, phenobarbital should be given as a loading protocol (see Box 3). This will cause stupor for the first few hours and the patient will need to be hospitalised for several days. Fluids and oxygen supplementation will be necessary during this period.

If phenobarbital loading is ineffective, a continuous rate infusion of propofol can be considered. Propofol has potent antiseizure properties and an intravenous bolus of 4 to 8 mg/kg can be given to effect. A continuous rate infusion can be given at 6 to 12 mg/kg/hour. This regimen should be used with caution. Animals are likely to be anaesthetised at these doses, so supportive care including oxygen and fluids will be necessary. If the patient is refractory to diazepam and phenobarbital, the prognosis for recovery is guarded.

What seizure frequency is acceptable?

There are no definite answers to this question. The effect of epilepsy on quality of life will depend on the severity and length of the seizures, and the character of the prodromal and postictal phases. Some dogs are very anxious or aggressive either pre- or post-seizure, and some animals may be temporarily blind or profoundly ataxic following a seizure. However, in certain patients, the quality of life may still be reasonable even with one seizure occurring every two weeks or more. Euthanasia is often considered if animals are having weekly seizures in the face of aggressive treatment. In such cases, owner communication is imperative.

Veterinary surgeons may be under pressure to treat dogs that have very infrequent seizures from owners who are struggling to cope with the risk of any seizures occurring at all. Communication and education are key, and, with better understanding, many owners can learn to live satisfactorily with an epileptic dog.

References and further reading


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