MANAGEMENT OF REFRACTORY CANINE EPILEPSY – PART TWO

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Categories : Vets

Date : December 10, 2012

MARK LOWRIE looks at drug therapies, studies evaluating antiepileptic medication and the effectiveness of diet in management of the condition

A PREVIOUS article (*VT*42.38) described the identification of epilepsy and the role of genetics in the aetiology and management of the condition.

This second part describes the numerous antiepileptic drug therapies available for management of idiopathic epilepsy. Additionally, it highlights the problems of how antiepileptic medication is evaluated in veterinary medicine and includes the results of studies that have attempted to minimise these problems. The role of diet in epilepsy is also discussed with mention of all the studies performed in veterinary medicine to date.

The perfect antiepileptic drug trial?

The main concerns an owner has when considering antiepileptic drug (AED) therapy are its efficacy and any relevant adverse effects that may result.

Adverse effects can be sporadic and, therefore, single case reports and large case series are collectively useful in collating information on potential adverse reactions that have been observed in the use of these medications for epileptic dogs.

However, information on efficacy can be a lot harder to gather. Most studies investigating the

efficacy of veterinary AEDs do not use a control population and, without this, the information regarding drug efficacy may be inaccurate.

A study reports that 30 per cent of epileptic dogs receiving a placebo had a 50 per cent or more reduction in seizure frequency (Muñana et al, 2010).

As this article will show, this response rate is similar to previously published reports of the efficacy of many of the commonly administered AEDs and draws into question their efficacy over a placebo. However, since publication of this information regarding a placebo, other studies have been designed that compare the efficacy of a novel AED against that of a placebo. These studies are small and some are in their infancy and as time progresses, the picture should become clearer as to which AEDs have the best effect.

Antiepiletic drug therapy

• Phenobarbital

Phenobarbital is licensed as a monotherapy for seizures in dogs and should be used as a first-line drug according to the cascade. The initial dosage is 2mg/kg to 3mg/kg twice daily, and serum concentrations reach steady state within 10 to 14 days (Podell, 2004). Therefore, it is advisable to check serum concentrations two weeks after starting the drug, with intra-patient consistency as to when this sample is collected in relation to timing post-pill (Monteiro et al, 2009).

To maintain therapeutic serum concentrations, subsequent increases in dose may be required. This is due to hepatic enzyme induction that decreases the elimination halflife of the drug (Hojo et al, 2002). The half-life of this drug is consequently very variable and is usually between 40 to 90 hours (Podell, 2004). Autoinduction, therefore, means it is imperative to check the serum phenobarbital concentration before assessing response to therapy.

Sedation and ataxia are common adverse effects seen with this medication, although they are usually transient and only persist in some cases. Polyphagia, polydipsia and polyuria are also frequently encountered and are usually dose-related.

Other side effects that occur with phenobarbital are classified as idiosyncratic as they seem to be neither related to dose nor prolonged administration. These include hyperexcitability, acute hepatotoxicity (Dayrell-Hart et al, 1991; Muller et al, 2001), which is different to the chronic progressive hepatopathy seen with chronic administration, blood dyscrasias (for example, thrombocytopaenia, anaemia or leucopenia; Jacobs et al, 1998; Weiss, 2005; Khoutorsky et al, 2008) and superficial necrolytic dermatitis (March et al, 2012).

Hepatotoxicity has been suggested to be dose-related and one study found dogs with hepatotoxicity had phenobarbital concentrations exceeding 40µg/ml. On this basis, it is

recommended phenobarbital serum concentrations should be maintained below 35µg/ml in an attempt to minimise this potential for hepatotoxicity. Pancreatitis has been reported in dogs treated with phenobarbital monotherapy or in combination with potassium bromide (Gaskill et al, 2000; Steiner et al, 2008).

It is also important to understand the normal laboratory changes induced by phenobarbital. The most common changes observed are asymptomatic mild to moderate elevations in serum alkaline phosphatase (ALP) and alanine transaminase (ALT; Dayrell-Hart et al, 1991; Muller et al, 2001).

Clinical signs of hepatotoxicity include anorexia, sedation, ataxia, icterus, and ascites (Dayrell-Hart et al, 1991; Muller et al, 2001). Laboratory evidence of hepatotoxicity includes proportionally larger increases of ALT compared to ALP activity. However, these increases cannot be used solely as a signal of underlying liver disease and a bile acid stimulation test is recommended as routine monitoring for dogs on phenobarbital (Dayrell-Hart et al, 1991; Muller et al, 2001).

Phenobarbital also causes a decrease in total thyroxine concentration that does not result in the clinical manifestation of hypothyroidism (Gaskill et al, 1999). Furthermore, a compensatory increase in thyrotropin concentration may be seen, making a diagnosis of hypothyroidism in dogs on phenobarbital sometimes challenging.

- **Potassium bromide**

Potassium bromide (KBr) is effective as a monotherapy in dogs, although it is most commonly used as an add-on therapy with phenobarbital in dogs (Podell et al, 1993). This product is only licensed for use as an AED therapy adjunct to phenobarbital in refractory cases of epilepsy in dogs.

Approximately one in four epileptic dogs that are phenobarbital-resistant achieves a seizure frequency reduction of at least 50 per cent when KBr is included to the management regime, according to one study (Podell et al, 1993).

Bromide competes with chloride at GABA receptors, hyperpolarising the neuronal membrane and increasing the seizure threshold. Bromide also competes with chloride for renal elimination and, therefore, sodium chloride intake must not be altered for dogs receiving this medication. Failure to achieve this will result in increased elimination or bromide toxicosis (Nichols et al, 1996).

Renal insufficiency also decreases bromide elimination and KBr should be used cautiously in these patients. Reported side effects of KBr include vomiting, weight gain, polyphagia, pancreatitis, polyuria and polydipsia.

Another disadvantage of using KBr is its long elimination half-life – approximately 25 days (Podell, 2004). Steady state is achieved only after three to four months of initiating therapy and this is important to remember when measuring the serum concentration because blood collection before

this time may give a sub-therapeutic serum concentration.

Occasionally, a loading dose may be necessary in dogs with frequent seizures (usually 600 mg/kg divided over five days) or when phenobarbital must be withdrawn due to liver disease. The major limitation of loading KBr is there is no time for tolerance to the sedative effects of the drug to develop. Therefore, lethargy and ataxia may be severe, vomiting may occur, and hospitalisation during the loading period is recommended. If loading is performed, a blood sample may be taken 24 hours later to assess the serum concentration.

• **Gabapentin**

As with many of the antiseizure medications in use, gabapentin was first used in people to control seizures.

Gabapentin is eliminated predominantly by the kidneys. Approximately one-third is partially metabolised by the liver, although there is no appreciable induction of the hepatic microsomal enzymes (Radulovic et al, 1995; Podell, 2004). Therefore, dose reduction may be required in dogs with renal insufficiency although no guidelines are available on this. The elimination half-life in dogs is two to four hours and it requires frequent administration to achieve steady state concentrations (Radulovic et al, 1995). The recommended oral dosage is 10mg/kg to 20mg/kg every eight hours (Platt et al, 2006).

The efficacy of gabapentin in the management of refractory canine epilepsy has been evaluated in two studies (Platt et al, 2006; Govendir et al, 2005).

The first study reported 11 dogs that were already receiving phenobarbital and potassium bromide at therapeutic serum concentrations and were deemed to have poor seizure control (Platt et al, 2006). Gabapentin was given as an add-on medication at a dose of 10mg/kg every eight hours. Six out of the 11 dogs had a seizure frequency reduction of 50 per cent or more within the first three months of beginning the medication. Furthermore, many of these dogs still had cluster seizure activity on multiple days. However, six dogs suffered side effects of ataxia and sedation, and in one patient this was deemed severe enough to cease therapy.

The second study evaluated 17 dogs with refractory seizures that were administered gabapentin at a dose of 35mg/kg/day to 50mg/kg/day divided twice or three times daily (Govendir et al, 2005). Sixteen of these dogs were receiving phenobarbital and potassium bromide, achieving therapeutic serum concentrations, whereas the final dog was receiving phenobarbital alone.

None of the dogs in this study experienced a reduction in seizure frequency of more than 50 per cent. There was no significant improvement in seizure frequency during the four-month study period. This may be because gabapentin was administered every 12 hours in most dogs included in this study. No significant reduction in seizures was seen across the whole cohort during the

study period. The side effects reported in both studies were sedation and ataxia.

There is no published infor mation on the longer-term efficacy of this medication or the potential for delayed adverse effects. The availability of generic gabapentin has made it affordable relative to other antiepileptic drugs used in veterinary patients and this is why it is still considered a therapeutic option.

• **Levetiracetam**

Levetiracetam is one of the more recently approved human AEDs and probably one of the more commonly used medications in the management of refractory canine epilepsy. Although generally recommended as an add-on AED it may be considered as a monotherapy.

Levetiracetam has minimal hepatic metabolism in dogs, with almost 90 per cent of the drug excreted in the urine and the remainder being hydrolysed in the serum and other organs. The half-life in dogs is three to four hours, which necessitates frequent administration (see Figure 1) and means steady state is reached within 48 hours (Patterson et al, 2008). The recommended oral dose is 20mg/kg every eight hours. No clear understanding exists of the relationship between serum drug concentration and efficacy so serum monitoring is not performed for this medication.

In a study of 14 dogs with refractory idiopathic epilepsy, six patients had a seizure frequency reduction of 50 per cent or more in the first two months after adding in levetiracetam (Volk et al, 2008). Increasing the dose to 20mg/kg every eight hours in the nonresponders allowed a reduction in seizure frequency of 50 per cent or more in only one dog.

Long-term toxicity data for levetiracetam in dogs confirm the drug is extremely safe. The drug was well tolerated by all dogs in the study and sedation was the only side effect, reported in just one of the 14 dogs. However, twothirds of the responders in this report experienced an increase in seizure frequency after four to eight months. Therefore, some dogs that initially improve on levetiracetam therapy may return to baseline seizure frequency after four to eight months – the so-called “honeymoon effect” (Volk et al, 2008).

Levetiracetam is also available in an intravenous formulation. One pharmacokinetic study has evaluated the disposition of the drug in six dogs after intravenous and intramuscular administration (Dewey et al, 2008).

A dose of 20mg/kg results in desirable serum concentrations within 40 minutes when administered intramuscularly, with no reactions seen. This drug may prove useful in treating cluster seizures and status epilepticus in dogs, with the option of administering the drug intramuscularly if venous access cannot be obtained.

The major drawback with this formulation is the high cost. Fryer et al (2011) have reported

intravenous leveteracetam was a good alternative to hepatically metabolised AEDs for the management of seizures associated with hepatic encephalopathy (Fryer et al, 2011; Figure 2).

Although not reported, this drug is gaining favour in the treatment of severe cluster seizures. It may be useful for dogs demonstrating cluster seizures that have numerous seizure episodes in 24 to 72 hours, but a relatively long inter-ictal period between clusters (usually weeks to months).

The short-term addition of levetiracetam for the duration of the cluster may reduce the number of seizures during the cluster. The drug can be used at a dose of 10mg/kg to 30mg/ kg every eight hours for the duration of the cluster (usually for two to three days) and then stopped when the dog has been seizure-free for at least 24 hours. This idea of “pulsedosing” has the advantage of reduced cost of medication and also appears to reduce the risk of tolerance.

Two studies reported in the past year are among the first to investigate AEDs using a suitable placebo control (Muñana et al, 2012; Hardy et al, 2012).

The first evaluated the efficacy of levetiracetam as an add-on therapy in dogs with poorly controlled IE (Muñana et al, 2012). Dogs were entered into an eight-week baseline assessment during which the owners recorded seizure activity. Thereafter, dogs underwent two 16-week treatment periods in which either oral levetiracetam (20mg/kg q8hours) or a placebo were administered.

The use of levetiracetam versus a placebo revealed no significant decrease in seizure frequency. Fifty-six per cent of dogs receiving levetiracetam were classified as responders (? 50 decrease in seizure frequency) versus 30 per cent receiving a placebo, but this difference was not significant.

The second study evaluated the use of intravenous levetiracetam compared to a placebo in the management of canine status epilepticus and cluster seizures of varying aetiology (Hardy et al, 2012). Nine of the 10 dogs receiving levetiracetam were considered responders (that is, no more seizures 24 hours after administration) versus just one in 10 dogs in the placebo group. However, sample size was small (19 dogs in total), and the placebo group contained five out of 10 dogs with symptomatic epilepsy versus only one in nine in the levetiracetam group. This is important, as symptomatic epilepsy has been found to be associated with a higher mortality (Batemann and Parent, 1999).

• Zonisamide

Zonisamide is one of the most recently approved human AEDs and is slowly finding its way into the management of canine refractory epileptic patients.

It has a half-life of approximately 15 to 20 hours, which is longer than many of the novel AEDs, and steady state is usually achieved within three to four days (Booth, 2008).

Zonisamide is metabolised in the liver by hepatic microsomal enzymes (cytochrome P450 and glucuronyltransferase) and its half-life is significantly shorter in patients receiving phenobarbital or any other drug that is metabolised by these enzymes. On this basis the current recommended starting dose is 5mg/kg every 12 hours if the patient is not receiving phenobarbital or 10mg/kg every 12 hours if used as an adjunct to phenobarbital treatment (Orito et al, 2008). Zonisamide is teratogenic in dogs and so its use should be avoided in pregnant animals.

Two different open-label studies have evaluated the use of zonisamide in dogs that report a decrease in seizure frequency of ? 50 per cent in seven of 12 dogs (Dewey et al, 2004) and nine of 11 dogs (Von Klopmann et al, 2007) for approximately two to four months following initiation of treatment.

Side effects were reported in around half the patients treated with zonisamide and included transient sedation, ataxia and vomiting. None of the adverse effects seen in these studies were considered severe enough to cease zonisamide therapy.

Two single case reports describe hepatotoxicity as a complication of zonisamide therapy (Miller et al, 2011; Schwarz et al, 2011). One study also describes the “honeymoon effect” in which zonisamide therapy is initially effective, but a return to baseline seizure frequency is seen after approximately six months (Von Klopmann et al, 2007). It should be made clear to owners that use of this medication in veterinary medicine has been limited and its effectiveness and potential side effects are not fully understood.

Dietary manipulation

Diets suggested for dogs with epilepsy include a simple hypoallergenic diet, a raw meaty bones diet, or the use of a ketogenic diet – low in carbohydrates and high in fat (Collins, 1994).

Despite many anecdotal reports of the value of some of these diets no placebocontrolled canine study or peer-reviewed literature exists to support or oppose these claims. However, introducing a dietary plan is simple, with minimal adverse reaction, and may provide benefit in an otherwise difficult situation. It should be used in conjunction with, and not as a replacement for, conventional AED therapy.

• Hypoallergenic diet

Some investigators suggest toxins and allergens in food may be epileptogenic (Collins, 1994). Therefore, the rationale behind a hypoallergenic diet is that avoidance of such proteins may alleviate these seizures.

The author is only aware of one veterinary study investigating the use of a hypoallergenic diet in canine epilepsy (Lujan et al, 2004). The study reported an unusually high incidence of allergic

disease. It included eight refractory epileptic dogs and seven were found to have gastrointestinal or skin allergies in conjunction with their refractory seizures. Introduction of an exclusion diet reduced seizures to an “acceptable level” in seven out of eight dogs. Behavioural abnormalities associated with seizures were completely eliminated in all cases.

Nothing further has been reported since this trial, but anecdotal reports support the idea of incorporating a hypoallergenic food trial into the regime of refractory IE dogs.

• **Raw meaty bones diet**

The argument for using a raw meaty bones diet stems from the belief that commercial diets may have certain deficiencies, which, over a long period of time, may lead to the development of epilepsy. This hypothesis has yet to be tested in veterinary epilepsy.

• **Ketogenic diet**

The rationale behind a ketogenic diet has been extrapolated from studies in humans that show inducing ketosis can decrease seizure frequency in children.

However, metabolism is different when comparing humans to dogs and the levels of ketosis easily induced in man cannot be induced in dogs by dietary manipulation (Puchowicz et al, 2000).

Furthermore, results of a ketogenic food trial for dogs with idiopathic epilepsy failed to demonstrate a difference in seizure frequency in dogs fed a high-fat, low-carbohydrate diet compared to dogs fed a control diet, although the number of dogs enrolled in the study was small (Patterson et al, 2005). This has not found a role in the management of canine epilepsy.

• **Essential fatty acid supplementation**

Supplementing fatty acids has been found to alleviate seizures in humans with epilepsy, including some of the symptoms associated with it, for example, behavioural change.

A study enrolled 15 dogs with idiopathic epilepsy that were poorly controlled with conventional medication (Matthews et al, 2011). A unique feature of this study was that it was one of the first studies on canine epilepsy to include a double-blinded, placebocontrolled, crossover method. Each dog had a 12-week trial phase receiving a placebo medication or an essential fatty acid supplement. The owners were unaware of which trial phase the dog was on.

The results found no difference in seizure frequency between the placebo and the fatty acid supplement. However, one individual had a dramatic reduction in seizures when receiving the fatty acid supplement whereas another had a marked decrease in aggressive behaviour.

Unfortunately, the number of cases and the short trial period mean no significant conclusions could be drawn.

Summary

Although phenobarbital and potassium bromide remain valuable first choice antiseizure drugs for dogs, a number of alternative drugs and therapies can be used as adjunctive (in refractory epilepsy) or sole therapeutic options (in patients with severe adverse effects to phenobarbital or potassium bromide).

The cost of these medications, the frequent dosing required (often three times a day) and possible development of tolerance have obvious disadvantages. However, when used correctly the results can be extremely rewarding. Most importantly, these drugs and methods do not replace the need to perform a thorough clinical and neurological examination and complete diagnostic investigation, including advanced imaging when it is available.

• Please note that some of the drugs mentioned in this article are not licensed for use in dogs.

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