Proceedings of the
World Small Animal Veterinary Association
Mexico City, Mexico – 2005

Hosted by:

Reprinted in the IVIS website with the permission of the WSAVA
Seizures are a common problem in veterinary medicine. Their treatment can be made complicated by multiple factors in the decision making process. These factors include the signalment of the patient, the likely or confirmed aetiology of the seizures, how long the patient has been seizing, how severe the seizures are, the drugs that are available to veterinary patients, the cost of the diagnosis and treatment options and the wishes of the owners.

Chronic seizure therapy is generally indicated for seizures that last more than 5 minutes, cluster seizures (for which there is no detectable inter-ictal period), or seizures that occur more frequently than once per month. Control of canine epilepsy is only possible in up to 70 – 80 % of cases on monotherapy. This therapy may improve if combination therapy is used. This treatment must be for initiated for the life of the animal. The most common anti-epileptic drugs (AEDs) used in veterinary medicine are phenobarbitone, primidone, diazepam, and potassium bromide. Other drugs found to be less useful include phenytoin and valproic acid. More recently, several human drugs, such as gabapentin, have been evaluated for seizure therapy in veterinary patients.

Phenobarbitone (PB)

Phenobarbitone is the drug used most commonly by veterinarians, as the drug of first choice for seizure control in dogs due to its low cost and approximately 80% success rate in controlling seizures in epileptic dogs.(3) This drug has been well documented to occasionally have fatal hepatotoxic effects in dogs as well as cause neutropenia. A good slow induction dosage of PB is 2-4 mg/kg/day divided BID or TID. If indicated, the dosage may be slowly increased to as much as 18-20 mg/kg divided BID or TID. Serum PB concentrations should be monitored to assess therapy. A PB serum concentration of 15-45 ug/ml should be achieved immediately prior to each subsequent dosage of medication. It will take 7 to 18 days to achieve a steady state serum concentration with sustained maintenance doses. If dosages of 4 mg/kg/day or higher are used to
initiate PB therapy, some dogs will appear depressed, drowsy or ataxic for about one month. This effect then generally resolves, and much higher doses can be given without sedation occurring. Some dogs will be polyuric, polydipsic and polyphagic while receiving PB, especially at higher doses. The serum alkaline phosphatase (AP) and the serum alanine transaminase (ALT) will increase in many dogs maintained on the drug. At least once/year, a PB serum concentration, serum chemistry profile, and haematology should be done on any animal receiving PB maintenance therapy. Any dramatic change in results from one year to the next may signal potential toxicity. This is the drug of choice in cats with multiple seizure episodes. The dose advised is 1.5 to 2.5 mg/kg PO every 12 hours. Due to the formulation of this drug, it is often best to start with 7.5 mg twice daily, which can be increased in 7.5 mg increments as necessary. Polyphagia with weight gain is documented as a frequent side-effect of PB administration in cats. Hepatotoxicity has not been documented in cats on this drug, but cutaneous hypersensitivities and bone marrow suppression have.

**Potassium bromide (KBr)**

Potassium bromide is becoming the drug of first choice for the management of epilepsy in dogs since it is the only anticonvulsant known that has no hepatic toxicity and all the adverse effects of KBr are completely reversible once the drug is discontinued. KBr controls approximately 80% of the epileptic dogs it is used to treat and is often effective in dogs that fail PB therapy. When high dose KBr and low dose PB are used together, approximately 95% of epileptic dogs can be controlled.

The maintenance dosage of is 20-100 mg/kg/day (which can be divided BID to avoid GI upsets) to achieve serum concentration of 1-5 mg/ml measured just before the next dose is administered. It requires 2 to 3 weeks of therapy before bromide serum concentration will enter therapeutic range and close to 4 months before steady state values are approximated. If seizure control is needed more rapidly than this, a total oral loading dose of 400 to 600 mg/kg of potassium bromide can be given prior to instituting the maintenance dosage schedule divided qid over 4-5 days. By dividing the loading dose, excessive sedation may be avoided in case the dog is especially sensitive to the sedative effects of bromide. The loading dosage should be mixed well with food to avoid the induction of vomiting. Be sure to stress to owners that it is important to keep the salt content of the diet consistent to prevent marked serum concentration fluctuations of bromide.

The most common adverse effect of bromide therapy is polyphagia, and it is recognized in about 25% of the dogs on therapy necessitating changing to a low calorie diet such as canine R/D or W/D to prevent excessive weight gain. Polydipsia and polyuria are less common with KBr therapy than with PB therapy, but these adverse effects are sometimes recognized. Personality changes that can occur are; irritability leading to snapping at people or other animals, seeking constant attention from the owner, aimless pacing behavior, and most commonly, depressed mental level as a result of sedation. Clinical signs of bromide toxicity are sedation, incoordination, and in dogs, pelvic limb weakness and/or stiffness is observed, easily misdiagnosed as pelvic limb stiffness.
due to osteoarthritis, since specific neurologic deficits are absent. Bromide toxicity can be seen in
dogs that have renal insufficiency because the halide ion is excreted by the kidneys. There has
been an association made between the use of bromide in cats and the onset of a reversible
respiratory disease.

**Primidone**

Primidone is metabolized in the liver to phenylethylmalonic acid (PEMA) and PB. Phenobarbital
levels should be monitored in dogs on primidone as they correlate better with anticonvulsant
efficacy than primidone levels. The same side-effects that phenobarbital create are seen with the
use of primidone. The target therapeutic ranges are also the same. Primidone is advised for use
in those patients who have proven refractory to phenobarbital although its efficacy has not been
proven. Otherwise there is no evident advantage of primidone over the use of PB as a first choice
AED. The conversion rate of primidone to PB is close to 4:1. Therefore the use of 250 mg of
primidone equals the use of 60mg of PB. Conversion from primidone to PB should take place
slowly (1/4 of the dose each month). In the dog, the use of this drug has resulted in progressive
hepatic injury, which seems to be more common than that seen with PB.

**Phenytoin**

This drug has anticonvulsant properties but is not a sedative. However, it has not been shown to
be an effective AED in the dog due to a failure in attaining therapeutic concentrations owing to its
short half-life and poor absorption from the canine GI tract. The short half-life means that there
has to be a high dosing frequency.

The use of phenytoin in combination with PB or primidone may lead to increased concentrations
of epoxide metabolites, which could result in cholestatic hepatic injury. There are now slow-
release preparations of phenytoin which need to be evaluated and may have some value in
canine seizure control.

**Diazepam**

Tolerance to the anticonvulsant effects of diazepam develops in 1 – 2 weeks in the dog. It
therefore has limited use in dogs. After prolonged treatment, abrupt withdrawal of diazepam can
elicit seizure or signs of withdrawal (shakes, anorexia, weight loss). The half-life of diazepam in
cats is nearly 20 hours, which is up-to 6 times longer than in dogs. The dose is 0.25 to 0.5 mg/kg
PO every 8 to 12 hours, incrementing 1 to 2 mg at a time to avoid the CNS side-effects such as
sedation. Unfortunately, the documentation of hepatotoxicosis as an adverse effect of the use of
this drug in cats makes its use less frequent than phenobarbital. Acute hepatic necrosis has been
seen as early as 5 days after initiation of the recommended doses of oral diazepam. Therefore,
the evaluation of liver enzymes 5-7 days after the initiation of diazepam in cats is recommended.

**Chlorazepate**
Tolerance seems to develop to this drug at a slower rate than with diazepam. Its use in dogs in conjunction with PB will increase the concentrations of PB. Start at 1mg/kg q12hrs orally and measure both PB and chlorazepate at 2 and 4 weeks. It has been useful for short-term breakthrough seizure control.

- Gabapentin (Neurontin)

Gabapentin is a recent addition to the human anti-convulsant market, which has primarily been used as an adjunctive drug for humans with uncontrolled partial seizures with and without secondary generalization. Gabapentin is well absorbed from the duodenum in dogs with maximum blood levels reached in 1 hour after oral administration. The elimination half-life of gabapentin in dogs is 3-4 hours in dogs, meaning that it may be difficult to attain steady state levels in dogs even with tid dosing. The dose at present estimated to be necessary to achieve some effect in dogs is 30 to 60 mg/kg divided tid to qid. It may be that its use in dogs demands higher doses making its expense prohibitive. In dogs, gabapentin is metabolised in the liver, therefore liver function needs to be closely evaluated when dogs are on this treatment; it is excreted nearly 100% through the kidneys, with 60% being the unchanged parent drug. The author has used this drug with no deleterious effects, in addition to PB and KBr. In a study of 11 dogs, 45% demonstrated improved seizure control with success based upon a 50% reduction in seizure frequency. However, many dogs still exhibited multiple days on which there was cluster seizure activity. Forty-five percent (5/11) of the dogs in this study also demonstrated sedation and ataxia after the addition of this medication. The therapeutic range documented is 4-16 mg/L, however long term efficacy and toxicity trials with this drug have not been done in the dog.

Levetiracetam

Levetiracetam was approved in November 1999 as a human add-on therapy for the treatment of partial onset seizures, with or without generalisation, in adults. Studies show that levetiracetam displays potent protection in a broad range of animal models of chronic epilepsy. Levetiracetam is water-soluble, is not metabolized by the liver, is excreted by the kidneys and is free of significant drug-drug interactions. The dose range documented for dogs is estimated to be 5-25 mg/kg q 8-12hrs PO. Levetiracetam has been documented as the most well tolerated anti-epileptic drug in humans, with adverse reactions equal to that of placebo. Overall, this drug is proven to be a highly effective adjunctive therapy in humans to control seizures refractory to treatment. The author presently has 10 dogs on this medication in addition to PB and KBr with initial promising effects in 5 of them.
Zonisamide

Zonisamide has an estimated elimination half-life of 15 hours in dogs, and has been administered twice daily (2-4 mg/kg) in 12 refractory idiopathic epileptic dogs with 58% of dogs responding favourably, experiencing a mean reduction in seizures of 81.3%. Five of the twelve (42%) dogs actually had an increased seizure frequency and 50% of the dogs exhibited side effects which included sedation, ataxia and vomiting.