Seizure Challenges: What drugs should we use?

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Abstract: The drugs available, the side effects and how to use them will be discussed for the management of dogs with difficult to control seizures. Adjunctive alternative approaches will also be discussed.

Keywords: Seizures, refractory, phenobarbital, bromide, levetiractam, zonisamide

Phenobarbital (PB)

Phenobarbital 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. 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.

Gabapentin

Gabapentin is a recent addition to the human anticonvulsant 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 metabolized 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.

Levetiracetam

Levetiracetam was approved in November 1999 as a human add-on therapy for the treatment of partial onset seizures, with or without generalization, 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 10-30 mg/kg q 8hrs PO. Levetiracetam has been documented as a well tolerated anti-epileptic drug, in both dogs and cats, with adverse reactions equal to that of placebo. Overall, this drug is proven to be effective adjunctive therapy to control seizures refractory to treatment. However, this may not be the case when used as monotherapy. In a recent study, 12 client-owned dogs were randomized to treatment with levetiracetam (30 mg/kg/day or 60 mg/kg/day divided into three daily dosages) or phenobarbital (4 mg/kg/day divided twice daily). Control visits were at days 30, 60 and then every 3 months for up to 1 year. Two or more seizures within 3 months led to an increase in drug dosage (levetiracetam: 10 mg/kg/day, phenobarbital: 1 mg/kg/day). Five of six levetiracetam treated dogs and one of six phenobarbital treated dogs withdrew from the study within 2–5 months due to insufficient seizure control. In the levetiracetam treated dogs there was no significant difference in the monthly number of seizures before and after treatment, whereas in the phenobarbital treated dogs there were significantly ($P = 0.013$) fewer seizures after treatment. Five phenobarbital treated dogs were classified as true responders (≥50% reduction in

seizures/month) whereas none of the levetiracetam treated dogs fulfilled this criterion. Adverse effects were reported in both groups but were more frequent in the phenobarbital group. Levetiracetam was well tolerated but was not effective at the given doses as monotherapy in dogs with idiopathic epilepsy!

Zonisamide

Zonisamide has been shown to be both effective for focal and generalised seizures in people. It is metabolized mainly by hepatic microsomal enzymes, and the half-life in dogs is approximately 15 hours. The dose suggested for use as an add-on drug in dogs is 10 mg/kg q12hrs PO. A high safety margin has been demonstrated with chronic dosing studies in dogs. A recent clinical trial has shown that the use of this drug has decreased seizure frequency by over 50% in approximately 50% of dogs on polytherapy, additionally enabling a reduction in the concurrent dose of PB. Five dogs had an increase in seizure frequency. Mild side effects(e.g., transient sedation, ataxia, vomiting) occurred in six of the dogs. Nine of 11 idiopathic epileptic dogs refractory to PB and or KBr responded to zonisamide in another study, with a mean of 70% reduction in seizure frequency. As for levetiracetam, seizure control was noted to subside after a couple of months in several dogs on zonisamide. In a recent study evaluating this drug as a monotherapy, oral zonisamide was administrated to 10 dogs with idiopathic epilepsy at 5-15 mg/kg PO every 12 h to achieve a concentration of zonisamide in serum of 10-40 μg/mL. The frequency of seizures before and after the administration of zonisamide therapy was recorded. Six (60%) of the dogs were favorable responders to treatment, showing a ≥50% reduction in monthly frequency of seizures. Of the remaining four, two dogs did not show a reduction and the other two showed an increase in frequency of seizures. The mean dosage of zonisamide for favorable responders was 7.92 (SD 3.79) mg/kg, which was administered orally twice a day.

Only one dog, which was one of the unfavorable responders in the whole study, experienced mild side effects.

Pregabalin

Pregabalin like gabapentin is a structural, but not functional analogue of the neurotransmitter gamma-aminobutyric acid (GABA). Pregabalin has shown greater potency than gabapentin in preclinical models of epilepsy and pain in people. Pregabalin is active in a number of animal models of epileptic seizures including maximal electroshock-induced tonic extensor seizures in mice and rats, hippocampal kindled rats and threshold clonic seizures from the convulsive agent pentylenetetrazol and genetic mouse models, with a greater potency than gabapentin. There is no protein binding or hepatic metabolism, it is renally excreted with no drug-drug interactions identified. Eleven client-owned dogs suspected of having idiopathic epilepsy that was inadequately controlled with phenobarbital, potassium bromide, or a combination of these 2 drugs were treated with pregabalin (3 to 4 mg/kg PO, q 8 h) for 3 months. Seizures were significantly reduced (mean, 57%; median, 50%) after pregabalin administration in the 9 dogs that completed the study; 7 were considered responders with mean and median seizure reductions of 64% and 58%, respectively. Pregabalin may hold promise as a safe and effective adjunct anticonvulsant drug for epileptic dogs poorly controlled with the standard drugs phenobarbital or potassium bromide. Adverse effects of pregabalin appeared to be mild.

Imepitoin (IMP)

IMP, licensed in Europe in 2013 after approval by the European Medicines Agency (EMA), is the first anticonvulsant drug specifically developed for the treatment of seizures in idiopathic epileptic dogs. IMP is claimed to have the same efficacy and fewer side effects than phenobarbital. A randomized, blind, controlled parallel group clinical field trial did not find any

significant differences in the monthly seizure frequency reduction and in the complete suppression of generalized seizures between IMP (75 per cent and 46.9 per cent, respectively) and phenobarbital-treated group of dogs (83 per cent and 58 per cent, respectively). The same study showed that the frequency of adverse effects was significantly higher in dogs treated with phenobarbital. IMP acts as a low affinity partial agonist at the benzodiazepine recognition site of the $GABA_A$ receptor. In contrast to full agonist drugs, such as phenobarbital, IMP does not seem to show tolerance, dependence and loss of anticonvulsant efficacy during prolonged treatment. No withdrawal signs have been noted following discontinuation of the treatment. The safety of IMP was evaluated under laboratory conditions on a group of healthy beagle dogs, in which no occurrence of relevant adverse events was detected after the administration of 0, 30, 90 or 150 mg/kg IMP every 12 hours for 26 weeks.

IMP was recently demonstrated to be efficacious in 54 per cent of treated dogs and produced a seizure-free state in 25 per cent of dogs at the end of the 12-month follow-up. The optimal minimum dosage was assessed to be ≥19 mg/kg every 12 hours. At the six-month follow-up, the reduction of the monthly seizure frequency was 52 per cent, and 21% were seizure free.