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Next WSAVA Congress:

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Control of canine epilepsy may only be possible in up to 70-80% of cases on phenobarbitone (PB). This therapy may improve if combination therapy with potassium bromide (KBr) is used. More recently, several human drugs, such as gabapentin and levetiracetam, have been evaluated for seizure therapy in veterinary patients. This article will discuss anticonvulsant drug use in dogs with so-called ‘refractory’ or ‘intractable’ epilepsy. Using multiple anti-convulsive drugs has several potential disadvantages, including the increased cost, the need to monitor and to interpret serum concentrations of multiple drugs, potential drug interactions, and more complicated dosing schedules. Indications for such ‘polytherapy’ include failure of diligent monotherapy and the treatment of cluster seizures. Before polytherapy is started, all reasonable options for monotherapy should be tried. If the initial drug is ineffective, a second drug should be added. If the dog responds, the veterinarian should attempt to withdraw the first drug gradually and continue with polytherapy if this is unsuccessful.

**Potassium bromide (KBr)**

Potassium bromide has no known hepatic toxicity and all the adverse effects of KBr are completely reversible once the drug is discontinued. Potassium bromide is excreted unchanged in the urine and is not metabolised by the liver. There have been no liver enzyme alterations or thyroid axis effects after administration of this drug. KBr controls approximately 70-80% 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 starting maintenance dosage of KBr is 20-30 mg/kg/day (which can be divided up to avoid GI upsets). 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. The target range is approximately 1-2 mg/mL when used concurrently with phenobarbitone and 2-3 mg/mL when used as monotherapy. However, some dogs can tolerate levels as high as 4 mg/mL; the maximum dose is always dictated by the patient’s clinical response. The bromide levels can be measured 4 weeks after the start of therapy at which time, drug concentrations will be approximately half of what they will be at steady state and the dose can be proactively changed early rather than waiting for another 2-3 months. The levels should also be measured at 4 months after starting bromide therapy when they will be at steady state. When PB is initially used, the dose of PB can be reduced gradually once or if the seizures are well controlled. Phenobarbitone may be completely discontinued in about 20% of dogs. If dogs need to be maintained on the two drugs, nearly 50% can have adequate seizure control with serum PB concentrations <20 µg/ml and lower bromide concentrations are needed when compared to the use of KBr as a monotherapy.

If seizure control is needed more rapidly, a total oral loading dose of 450-600 mg/kg (plus the recommended maintenance daily dose of up to 45 mg/kg/day) of potassium bromide can be given, prior to instituting the maintenance dosage schedule, divided qid over 4 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 dose should establish steady-state concentrations immediately. The loading dosage should be mixed well with food to avoid the induction of vomiting. Plasma drug levels should be measured after loading to evaluate the loading dose. After this the patient is continued on a daily maintenance dose of 30-45 mg/kg. One month later the drug should be monitored again. 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. In dogs fed high chloride diets such as some prescription diets, serum bromide levels should be monitored carefully. Renal insufficiency decreases bromide elimination; thus, in dogs with persistent isosthenuria or azotaemia, the initial dose should be halved and serum bromide concentrations monitored closely to avoid toxicity.

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. However, this side-effect can decrease with time. 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
is free of significant drug-drug interactions; therefore, metabolized by the liver, is excreted by the kidneys and of animal models of chronic epilepsy. Levetiracetam is not metabolized by the liver, is excreted by the kidneys and is free of significant drug-drug interactions; therefore, this is potentially a very safe drug to use in dogs. The dose range suggested for dogs is 10-20 mg/kg PO tid. The lowest dose is preferred, as like gabapentin, it is expensive. No therapeutic range has been established as yet and there are no long-term trials evaluating the safety and efficacy of this drug, however, a recent short-term clinical trial demonstrated that the use of this drug as a third anticonvulsant decreased seizure frequency by over 50% in epileptic dogs. Nine out of 14 dogs in another study were classified as levetiracetam-responders, but 6 of the 9 responders experienced an increase in their seizure frequency and seizure days after 4-8 months. In two initial responders the dose was increased with positive effect. One possible explanation put forward by the authors is that the dogs developed tolerance to the levetiracetam treatment. Intravenous and intramuscular levetiracetam has been investigated recently, demonstrating that these routes of administration are well tolerated and result in favorable pharmacokinetics, which may be useful in more emergent cases. The next generation of this drug currently undergoing clinical trials in people is brivaracetam.

**Gabapentin**

Gabapentin has primarily been used as an adjunctive drug for humans with uncontrolled partial seizures with and without secondary generalization, although it has had only modest success. 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 with tid dosing. The dose at present estimated to be necessary to achieve some effect in dogs is 10-20 mg/kg PO tid. 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 as a third drug for dogs refractory to PB and KBr. One study found that the addition of gabapentin to PB and / or KBr increased the inter-ictal period and shortened the post-seizure recovery in some canine epileptics. In some dogs, seizures were prevented completely while in others there was an increase in interictal period. A further study demonstrated that just over 50% of dogs had at least a 50% reduction in seizure activity. After addition of gabapentin both the number of seizures per week and the number of days with any seizures in a one-week period were significantly reduced. Mild sedation and ataxia have been noted as side effects.

**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.

**Topiramate**

The precise mechanism by which topiramate exerts its anticonvulsant effect is unknown; however, it increases the frequency at which γ-aminobutyric acid (GABA), a major inhibitory chemical of the central nervous system, activates GABA<sub>A</sub> receptors, and enhances the ability of GABA to induce a flux of chloride ions into neurons. In healthy beagle dogs, peak plasma concentration occurs between 0.6 and 3.8 hours. There was no evident accumulation and no autoinduction or inhibition of enzymes that metabolize topiramate resulting
from multiple dosing. Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine and when it was co-administered with PB in human studies, there was less than 10% change in the plasma concentration of PB. The most commonly observed side effects in humans associated with the use of topiramate, were somnolence, dizziness, ataxia and speech disorders. In renally impaired patients it is advised to administer half of the recommended dose, due to the renal elimination. No adverse reactions have been reported in dogs studied using 10-150 mg/kg daily oral doses for 15 days. Presently, the author is using this drug at 2.5-5 mg/kg PO tid but at this stage there is not enough data to know how effective this treatment will be.

**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 pentylentetrazol 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. Although a prospective study is currently underway evaluating the use of this drug in dogs with refractory epilepsy, no current data exists on its effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life in dogs (hr)</th>
<th>Oral dosage (mg/kg)</th>
<th>Concerns</th>
<th>Documented veterinary success as 3rd drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>3-4</td>
<td>10-20 tid</td>
<td>Sedation / liver metabolism / expensive</td>
<td>Approximately 50%</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>3.5</td>
<td>10-20 tid</td>
<td>Expense</td>
<td>Approximately 50%</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>15</td>
<td>10 bid</td>
<td>Expense</td>
<td>Approximately 50%</td>
</tr>
</tbody>
</table>

Table 1: Half-lives, dosages and documented successes of tertiary anti-convulsant drugs in dogs.