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# Six of the Best - Neurological Case Headaches Mini Series

## Lecture 1: Seizures - So Many Drugs, Which one Should I Use?
## Lecture 2: Emergency Seizure Control

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**The Drugs we use for Seizures and What to Expect**
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Management of epilepsy in cats and dogs often requires a lifetime commitment by owners. The owner must be willing to medicate their pet several times per day, travel to emergency clinics at unpredictable times, follow up with periodic re-evaluations and diagnostic testing, and watch their pet carefully for adverse effects of therapy.

The balance between quality of life and therapeutic success is often a key issue for an owner to continue treating their pet. Despite all of the time, financial and emotional commitment, a significant portion of dogs may still continue to have seizures. Thus, proper client education is critical in preparing owners for understanding their pet's condition and the potential associated lifestyle changes. In particular, the owners need to know that the diagnosis of epilepsy implies an increased risk of premature death with the prognosis dependent on a combination of veterinary expertise, therapeutic success, and the owner's motivation.

**Decision Making Strategies for AED Therapy**

The decision regarding when to start AED treatment is based on a number of factors, including etiology, risk of recurrence, seizure type and its effect on patient, as well as risk of treatment. Risk factors for seizure recurrence are not well-established for cats and dogs. A number of relative risk factors have been identified in epileptic people, to include a diagnosis of current or previous defined cerebral lesions or trauma, presence of interictal EEG epileptic discharges (up to 90 % recurrence rate) and a history of marked post-ictal adverse effects (Todd's paralysis).

Evidence-based guidelines through several international groups are well established for people based on risk: benefit ratio and predictability factors of drug effect. From these guidelines, several commonalities exist in guiding clinical practice to include confirmation of an epileptic seizure event and seizure type, obtaining a definitive diagnosis, knowledge that recurrent seizure activity is correlated with poorer long term treatment success, and the influence of treatment on quality of life factors. Thus, the decision to treat is a reflection of the treatment goals to reduce or eliminate epileptic events, reduce seizure severity, avoid adverse effects, and reduce seizure-related mortality and morbidity.

**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.(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.

**Gabapentin**

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.

**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.

**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.

**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. 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.

## CLUSTER SEIZURES AND STATUS EPILEPTICUS

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The goals of anticonvulsant therapy in SE are to achieve cessation of clinical and electrical seizure activity and prevent its recurrence. Intravenous drug treatment for SE should be started without delay. This is necessary based upon the relationship between duration of SE and the extent of neurologic morbidity. This approach is also based upon experimental animal models that suggest that SE becomes progressively less responsive to treatment with diazepam.

Benzodiazepines (diazepam, lorazepam, midazolam, and clonazepam) are potent, fast-acting anti-epileptic drugs (AEDs) and therefore (particularly diazepam), are the preferred initial therapy in SE. None of the benzodiazepines are effective for chronic control of SE. They are a widely used class of sedative/tranquilizer and anxiolytic agents that differ widely in their time course and their central effects. These differences may be related to their pharmacokinetics, especially their distribution into and out of the central nervous system, which has been related to the drugs' lipophilicity and plasma protein binding. The lipophilicity of these compounds determines their rapid brain penetration after intravenous administration. Although the penetration is rapid, distribution equilibrium among all regions takes longer. Adverse effects of intravenous benzodiazepines include respiratory depression, hypotension, and impaired consciousness. However, it has been suggested that there is a low incidence of respiratory depression with benzodiazepines because of the low density of binding sites in the brainstem.

### Diazepam

Diazepam remains the first drug of choice for the treatment of SE in dogs and cats. The major metabolites of diazepam, nordiazapam (desmethyldiazepam), and oxazepam have up to 33% of the activity of the parent drug. The half-life of diazepam is 3.2 hours in the dog but the half-lives of the metabolites are slightly longer, up to 5.2 hours in the case of oxazepam. With its relatively brief duration of action, diazepam is not a definitive therapy for SE. However, because in IV diazepam produces transiently high serum and brain concentrations of the drug, it can be a useful drug therapy. Because SE may end spontaneously, IV diazepam should not be administered to a patient presenting in a post-ictal state unless there is another seizure.

It has been recommended to use 0.5 to 1.0 mg/kg intravenously, up to a maximum dose of 20 mg, in dogs and cats. This dose can be repeated to effect or twice within two hours. If the diazepam does not control the seizures, the use of phenobarbital should be considered. Probably the most common and most dangerous error made in the management of SE is to treat repeated seizures with repeated doses of IV diazepam without administering an adequate loading dose of a longer-acting anti-epileptic drug. In this situation, the patient will continue to have seizures, toxic concentrations of diazepam or diazepam metabolites will accumulate, and serious morbidity may result from diazepam over-dosage. Intravenous administration of diazepam may not be possible in some patients. It can be administered intramuscularly (IM), although absorption is not predictable. Rectal administration of diazepam may be considered initially at a dose of 0.5 to 2.0 mg/kg body weight depending upon whether the animal was being treated with phenobarbitone before the onset of SE. It may be necessary to use the higher dose in dogs receiving long-term phenobarbitone therapy. In previously untreated dogs, a per rectum diazepam dose of 1 mg/kg results in a mean time to peak plasma concentration of approximately 14 minutes.

**Midazolam**

Midazolam is a recently developed water-soluble benzodiazepine which is biotransformed by hepatic microsomal oxidation followed by glucuronide conjugation. Midazolam has been shown to have a wide margin of safety and a broad therapeutic index. It will diffuse rapidly across the capillary wall into the central nervous system and can be mixed with saline or glucose solutions. The mean plasma elimination half-life in dogs was shown to be 53 –77 minutes following IV administration. Midazolam has a significant antiepileptic effect in humans proven to be caused by GABA(A) receptor stimulation, and has been shown to be more effective and safer for the control of seizures than comparable doses of diazepam. Unlike diazepam, with erratic and incomplete intramuscular absorption, midazolam is rapidly absorbed following IM injection, with a high bioavailability, an early onset of sedation, and early clinical effects. The peak plasma concentration in dogs after IM administration was seen within 15 minutes. The dose for cats and dogs is 0.066 - 0.3 mg/kg IM or IV.

**Phenobarbital**

Phenobarbital (PB) is a safe, inexpensive drug that may be administered orally, intravenously or intramuscularly. Phenobarbital increases the seizure threshold required for seizure discharge and acts to decrease the spread of the discharge to neighboring neurons. The distribution of PB to the central nervous system may take up to 30 minutes, because of weaker lipophilicity in comparison with diazepam. This will need to be considered if the animal is still exhibiting generalized seizure activity. The recommended loading dose is 12 to 24 mg/kg IV, if immediate therapeutic concentrations are desired but this can induce a profound stupor with concurrent suppression of the cardiovascular and respiratory. Alternatively, the dose can initially be 2 mg/kg IV, repeating the dose every 20 - 30 minutes to effect and to a maximum total 24-hour dose of 24 mg/kg. The parenteral form can also be given IM, which is recommended if diazepam has already been administered. This will avoid the potentiation of profound respiratory and cardiovascular depression. The depressant effects of PB on respiratory drive, level of consciousness, and blood pressure may complicate management of the SE patient, especially when administered after benzodiazepine. For these reasons, tracheal intubation may be necessary during IV administration of PB.

**Treatment of Refractory SE**

Status epilepticus that does not respond to a benzodiazepine or PB is considered refractory and requires more aggressive treatment. Potential reasons for resistant seizure activity include inadequate anticonvulsant doses, an uncorrected metabolic abnormality or the presence of an intracranial disease, such as a tumor. These patients often represent a difficult therapeutic problem. Short-acting anesthetic drugs are the most commonly used agents for treating resistant SE, as they have a rapid onset of action, short half-lives, and cause reductions in cerebral metabolic rates. These drugs should be used only in an intensive care setting because of the need for continuous blood pressure monitoring and ideally, central venous pressure monitoring.

**Continuous Diazepam Infusion**

This has been shown to be an effective mode of therapy in refractory SE in human and veterinary patients. The dose should be calculated hourly (0.1 to 2.0 mg/kg of body weight, q 1hr) and is usually diluted in 0.9% saline or in 5% dextrose in water (D5W), with the volume used being equal to the maintenance fluid requirement over the hour. The dose can be delivered with an infusion pump. The dosage rate should be reduced by 50% every 4-6 hours for at least 2 reductions before discontinuing the drug. Midazolam is completely water-soluble and has also been shown to be an effective and safe therapy when administered by constant rate infusion.

**Propofol**

In human cases of refractory SE, the use of IV infusions of anesthetic doses of propofol, 2,6-diisopropylphenol, has become standard. This approach has recently been evaluated in veterinary patients. Propofol has barbiturate- and benzodiazepine-like effects on the (GABA)A receptor and can suppress CNS metabolic activity. Propofol can be administered by IV bolus (1-4 mg/kg) or by constant rate infusion (0.1-0.6 mg/kg/min titrated to effect or up to 6 mg/kg/hr). The advantages of this drug over the barbiturates are its rapid clearance, chiefly eliminated by hepatic conjugation to inactive metabolites, and less profound hypotensive effects. However, this drug should be used with caution, preferably in settings where definitive airway control and hemodynamic support is possible, as hypoxemia secondary to apnoea is a primary side-effect as is myocardial depression.

**Barbiturates**

Thiopental and pentobarbital have potential, though unproven, cerebral protective effects in the management of SE. In adequate doses these drugs will almost always control the physical manifestations of seizures, but severe hypotension limits their safety. Pentobarbital sodium, used at standard safe doses, is a general anesthetic with negligible anticonvulsant properties. Thiopental has been associated with a higher degree of cardiac toxicity than pentobarbital. Pentobarbital should be given to effect not as a specific dose (3-15 mg/kg body weight IV) as there is tremendous individual variation in response. Patients treated with “barbiturate coma” commonly require an extended period of mechanical ventilation in an intensive care setting. In general, the side effects of barbiturate coma include depression of myocardial metabolism, vasodilatation with a decrease in venous return, and decreased cardiac perfusion. These effects can be minimized by the use of saline infusion and small doses of dopamine. Patients can develop poikilothermia and decreased urinary output during myocardial depression and hypotension. Neurologic evaluation is difficult because spontaneous respiratory responses and spontaneous movements cease. The reduced availability of an economically feasible, sterile formulation of these medications limits their use in veterinary medicine.

**Levetiracetam**

Levetiracetam is the *S*-enantiomer of the ethyl analogue of piracetam that has broad-ranging, unique but incompletely understood mechanisms of action against seizures. Its main mechanism may be in decreasing the onset of a seizure through enhanced GABA activated $Cl^-$ conductance. The pharmacodynamic effect is believed to outlive the known half-life of the drug. In dogs, this drug has a half-life is approximately 4-6 hours, is liver cytochrome P450 independent and is excreted unchanged by the kidneys. 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. In 2006, levetiracetam was approved in humans as the first of the newer anticonvulsive drugs for intravenous administration and has been trialed for its use with status epilepticus. It has been shown that it is an effective drug in people with this condition and is well tolerated at high doses. Recent pharmacokinetic studies in dogs have demonstrated that IV administration of this drug is well tolerated when administered as a bolus at 60 mg/kg and rapidly achieved suggested therapeutic levels. Clinical veterinary trials are underway for this drug.

**Ketamine**

Experimental animal work has indicated that NMDA glutamate receptor antagonists may be used to treat the so called self-sustaining status epilepticus (SSSE). This type of status exists after approximately 10 minutes to 1 hour and may have a different underlying pathophysiology

to that of the initial SE in that NMDA receptors may be over stimulated by excessive glutamate concentrations. Ketamine is a NMDA receptor antagonist which has been used in humans with refractory or SSSE and has been shown to be effective  in a dog with SSSE.

**Inhalational Anesthesia**

Inhalational anesthetics have been recommended as a last resort in cases of resistant SE. The equipment and personnel necessary to administer inhalational anesthesia may not be readily available and can be cumbersome. Isoflurane, an inhalational general anesthetic agent, may be efficacious in the treatment of resistant SE. Not all of the volatile anesthetic agents have anti-epileptic potential, however; enflurane may actually increase seizure activity. Isoflurane does not undergo hepatic metabolism, has a rapid onset of action and has been extensively studied. Obviously, isoflurane therapy necessitates ventilation and intensive-care monitoring, and hypotension may occur during therapy.