Managing Epileptic Dogs

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KEY FACTS

***** Poor seizure control may result from inaccurate diagnosis of underlying disease, insufficient client education, selection of an inappropriate antiepileptic medication or inadequate dose, and seizures that are refractory to standard therapy.
***** A thorough physical and neurologic examination as well as laboratory profile consisting of a complete blood count, serum chemistry profile, and urinalysis is indicated in any dog presented for evaluation of seizures.
***** Phenobarbital is the drug of choice for the initial management of idiopathic epilepsy in dogs.
***** Periodic reevaluation and therapeutic drug monitoring often are necessary to determine the dose of antiepileptic medication that controls the seizures and avoids side effects.
***** Administration of bromide improves control of seizures in many epileptic dogs that are refractory to phenobarbital.

Epilepsy generally refers to recurrent seizures of any cause, although many authors restrict the meaning to recurrent seizures unrelated to an underlying progressive disease. Successful management of epilepsy is often difficult as is evident by estimates that approximately 20% to 50% of canine epileptics treated at referral centers are not satisfactorily controlled. Factors that contribute to therapeutic failure include the presence of underlying disorders that cause the seizures or complicate management, insufficient client education, improper selection of medication and dose, intolerable side effects of medication, and seizures that are refractory to medication. This article discusses how to identify and avoid common causes of unsuccessful management of epileptic dogs.

INTENTIFYING UNDERLYING DISEASE

Epilepsy can be classified as idiopathic or symptomatic. Idiopathic epilepsy, also called primary or true epilepsy, is the most common type of epilepsy in dogs. The pathoshysiology of idiopathic epilepsy is incompletely understood, but a genetic defect in the neuronal membrane or neuro-transmitter function is suspected. Symptomatic epilepsy, also reffered to as acquired or secondary epilepsy is caused by previous or current intracranial or extracranial disease. Causes of intracranial disease may be congenital, neoplastic, inflammatory, traumatic, or vascular in origin. The principal extracranial disorders are caused by metabolic and toxic diseases (see Table I).

Table I Common Causes of Seizures in Dogs			
Age of Onset--	**<1 Year**	**1-5 Years**	**>5 Years**
Cause			
IDIOPATHIC EPILEPSY		**X**	
SYMPTOMATIC EPILEPSY			
Extracranial			
-Metabolic			
--Hypoglycemia			**X**
--Hypocalcemia		**X**	**X**
--Hepatic encephalopathy	**X**		**X**
--Hyperlipoproteinemia		**X**	**X**
-Toxic	**X**	**X**	**X**
■			
Intracranial			
-Developmental			
--Hydrocephalus	**X**		
--Lissencephaly	**X**		
--Metabolic storage diseases	**X**		
-Neoplastic			**X**
-Inflammatroy			
--Rabies	**X**	**X**	**X**
--Distemper	**X**	**X**	**X**
--Rickettsial diseases	**X**	**X**	**X**
--Protozoal diseases	**X**	**X**	**X**
--Fungal diseases	**X**	**X**	**X**
--Granulomatous Meningo-Encephalitis		**X**	
-Trauma	**X**	**X**	**X**
Vascular			**X**

Identification of an underlying intracranial or extracranial disease is extremely important. Therapy of seizures due to progressive disease requires not only medical control of seizures but management of the underlying disease. Because a definitive diagnosis of idiopathic epilepsy is seldom possible, the diagnostic approach is designed to identify any underlying disease.

The initial evaluation of any dog presented for evaluation of seizures should include a complete history; physical and neurologic examination; and laboratory profile consisting of a complete blood cound, serum chemistry profile, and urinalysis. Selection of other diagnostic tests should be based on the results of this initial evaluation.

HISTORY

Because many dogs presented for evaluation of seizures are normal on examination and laboratory evaluation, the history often is the most important component of the assessment. The age of onset is useful in narrowing the list of diagnostic differentials. In dogs with idiopathic epilepsy, the first seizure usually occurs between one and five years of age. When the onset of seizures occurs at younger than one year or older than five years of age, an underlying disease usually is responsible for the seizures.

Seizures can usually be classified as generalized or focal on the basis of the owner's description of the seizure. Generalized seizures, which are the most frequently recognized type, are usually characterized by unconsciousness, symmetric motor activity (e.g., opisthotonos or extension of the limbs followed by paddling and chewing movements) and autonomic signs (e.g., salivation, urination, and defecation). Milder generalized seizures sometime are recognized. With such seizures, the dog may remain conscious and have limited involuntary movement.

Focal seizures, also called partial seizures, are manifested by asymmetric motor activity (e.g., twitching of one side of the body) or bizarre, complex behavior (e.g., tail chasing, 'fly biting', or aggression). Consciousness may or may not be impaired during the focal seizure. A total seizure may progress to a generalized seizure. Classification of seizures is important because focal seizures usually indicate the presence of an underlying disease.

The history may provide evidence of a previous or current disorder that is responsible for the seizures. The owner should be questioned about illnesses or trauma, the possibility of intoxication, and vaccination history.

Physical Examination

Many underlying metabolic, infectious, and neoplastic diseases may be detected by careful physical examination, which includes examination of the ocular fundi. The neurologic examination should include assessment of behavior and gait, procrioception of all limbs, and cranail nerves (including the menace response to each eye and conscious facial sensation). Asymmetric deficits, such as circling, hemiparesis, blindness in one eye, or decreased sensation on one side of the face strongly suggest a focal intracranial lesion, such as neoplastic, inflammatory, or vascular disorders.

Generalized deficits suggest an extracranial or diffuse intracranial disorder. Because transient generalized deficits, such as blindness, depression, and ataxia, may rsult from any seizure (even i9n dogs with idiopathic epilepsy), the examination should be repeated if generalized abnormalities are detected soon after a seizure. Dogs with idiopathic epilspesy do not have interictal neurologic deficits.

Laboratory Examination

A complete blood cound, serum chemistry porfile, and urinalysis are indicated primarily to detect metabolic disorders. Liver function tests, such as serum bile acids or blood ammonia concentrations, should be performed if hepatic encephalopahty is suspected. Blood led evaluation is indicated in young dogs and dogs from areas with a high incidence of lead

poisoning.

Additional Diagnostic Tests

Other diagnostic procedures, such as radiography and serum titers for infectious diseases, may be indicated based on the initial evaluation. Computed tomography or magnetic resonance imaging is indicated in dogs older than five years of age and in dogs with persistent neurologic deficits; these procedures are able to detect intracranial lesions, such s tumors. Cerebrospinal fluid analysis should be considered ot detect inflammatory disorders in dogs younger than one year of age and in dogs with persistent neurologic deficits. Computed tomography or magnetic resonance imaging should precede cerebrospinal fluid collection in dogs suspected intracranial masses because removal of cerebrospinal fluid from dogs with increased intracranial pressure can cause dangerous shifts in brain tissue.

Diagnosis of idiopathic epilepsy is appropriate in dogs that have (1) generalized seizures, (2) an onset of seizures between one and five years of age, (3) no abnormalities on physical and neurologic examination, and (4) normal laboratory evaluations. Idiopathic epilepsy is always a tentative diagnosis; if other abnormalities develop or if seizures become unresponsive to therapy, the diagnosis should be reconsidered.

PERCIPITATING FACTORS

Concurrent disease, stress, or drug administration may complicate the management of epileptic dogs. Infections or metabolic disturbances may increase seizures activity in an otherwise well-controlled epileptic. Because estrogen increases susceptibility to seizures, estrus may provoke seizures in some epileptic dogs. Some medications, including phenothiazine tranquilizers, ketamine, and ivermectin, any increase seizure activity. Changes the dog's normal routine, such as travel, may cause sleep deprivation, which has shown to precipitate seizures in humans. A previously well-controlled epileptic should be evaluated for precipitating factors if seizures suddenly increase.

INSUFFICIENT CLIENT EDUCATION

Insufficient client education may result in client anxiety, unrealistic expectations, or noncompliance. The decision to begin drug therapy should be based on the frequency and severity of seizures and the owner's concerns. Because epilepsy refers to recurrent seizures, the term is correctly applied only after more than one seizure has occurred. In dogs with idiopathic epilepsy, treatment after the second seizure should be considered because early treatment may improve the prognosis for successful control of epilepsy. Some authors recommend antiepileptic drug therapy for dogs with seizures that occur more frequently than every four to eight weeks, episodes of status epilepticus, or clusters of several seizures daily.

Before drug therapy is started, the owner should understand the goals of therapy, potential side effects, and the cost and effort involved in managing an epileptic dog. Although completely eliminating seizures is ideal, a more realistic goal of therapy is to decrease the frequency and severity of seizures without causing unacceptable side effects. Many antiepileptic drugs cause mild sedation, polydipsia, polyuria, and polyphagia. The sedative effect usually diminshes after several weeks of therapy. Unless informed of the nature of these side effects, owners may become alarmed and stop therapy or reduce the dose.

Owners should also understand that several weeks of therapy are usually required to achieve a therapeutic serum concentration and that it is unrealistic to expect immediate reduction in

seizure activity. Periodic evaluations and dose adjustments usually are required to achieve optimum effects. Long-term therapy with most antiepileptic drugs, especially at high doses, can produce hepatotoxicity that may limit therapy. Owners must understand that their dogs may require daily medication for the remainder of their lives. Maintenance antiepileptic drug therapy is inappropriate if the owner is unable or unwilling to commit the necessary time, effort and expense.

INEFFECTIVE DRUGS

The choice of antiepileptic drugs ideally should be used on results of well-controlled clinical studies. The sporadic natural history of seizures, subjective criteria, I usually used to evaluate efficacy, and the reluctance to withhold therapy in lieu of a placebo have precluded well designed clinical trials. Nevertheless, ased on clinical experience and pharmackinetic data, phenobarbital is currently considered the drug of choice for the initial management of epilepsy in dogs. Primidone is also effective but may be more likely to cause hepatotoxicity. The short half-lives of thenytoin, carbamazepine, diazepam and valproic acid in dogs limit their use as single agents for the control of canine epilepsy.

INADEQUATE DOSE

One of the most common causes of poor seizure control is a dose that is too low. The oral dose of phenobarbital or primidone correlates poorly with serum concentrations because of variability in metabolism among dogs. Ideal management therefore requires measuring serum concentrations in each patient to help determine the proper dose.

The serum concentration should be measured when a steady state has been reached (that is, when the amount of drug eliminated is replace by drug being administered). After starting therapy or after any change in dose, five to six half-lives are required to achieve a steady state. Thus, for phenobarbital, serum concentration should be measured during the second week of therapy and two weeks after any change in dose. Therapeutic monitoring also should be done when there are signs of toxicity or poor seizure control; in addition, routine monitoring should be done every six months.

An adjustment in dose can be made based on analysis of serum collected immediately before the next dose (i.e., through concentration). If the seizures are poorly controlled and the serum concentration is low, the owner should be questioned to make sure that the dog is consistently receiving the recommended dose. If compliance is good, the dose should be increased. For drugs that are cleared by first-order kinetics (e.g., phenobarbital), the new dose can be calculated by the following formula:

New dose - Current dose x (Target Concentration / Measured concentration)

The target range for phenobarbital is 20 to 45 micrograms/ml (see Table II). Although monitoring serum concentrations is a useful guide, target ranges are average values and seizure control and side effects should be assessed carefully on an individual basis. Rigid adherence to the target range should be avoided. Some dogs may be managed well with serum concentrations below the expected target range; others may suffer unacceptable side effects at serum concentrations within the target range.

Table II
Antiepileptic Drugs for Dogs

Drug	Dose Regimen	Time to Reach Steady State	Target Serum Concentration
Phenobarbital	2-5 mg / kg 2 times / day	10-18 days	20-45 microgram / ml
Primidone	5-10 mg / kg 3 times / day	10-18 days	20-45 microgram / ml (phenobarbital *c)
Potassium Bromide	20 mg / kg 1 time / day	4 months	0.7 - 1.9 mg / ml (bromide *c)
Chlorazepate	2 mg / kg 2 times / day	NA*b	500-1900 ng / ml *d (nordiazepam *c)
Valproate	60 mg / kg 3 times / day	NA*b	50-150 microgram / ml *d
Mephenytoin	10 mg / kg 3 times / day	5-7 days	25-40 microgram / ml *d (5 - phenylhydantoin)

**a). Currently, primidone and phenytoin are the only drugs labeled for the treatment of canine epilepsy. Other antiepileptic drugs must be used in an extralabel fashion. Bromide must be custom formulated, and suppliers may require the veterinarian to contact the U.S. Food and Drug Administration.*

**b). Not applicable; steady state is not reached at the indicated dosage frequency.*

**c). Represents the active metabolite or compound that should be measured.*

**d). Human values; canine values are not known*

HEPATOTOXICITY

Occasionally, the development of hepatotoxicity complicates management of epileptic dogs. Most dogs receiving long-term antiepileptic drug therapy have moderate increases in serum alkaline phosphatase (SAP) and alanine transaminase (ALT) without serious liver dysfunction. Less commonly, severe and even fatal hepatotoxicity occurs. With the use fo phenobarbital, prolonged serum concentrations of greater than 35 micrograms/ml may increase the risk of serious liver disease.

A physical examination, complete blood count, serum chemistry profile, serum phenobabital concentrations, and bile acids should be assessed every 5 to 12 months in dogs receiving phenobarbital or primidone. Evidence of hepatotoxicity includes lethargy, ataxia, icterus, ascites, decreased albumin, proportionatley larger increases in alanine transaminase than serum alkaline phosphatase, increased bile acids and rising serum concentrations of phenobarbital despite a constant oral dose. If hepatotoxicity is suspected, potassium bromide should be used instead of phenobarbital. If phenobarbital is discontinued early enough, liver changes are potentially reversible.

REFRACTORY EPILEPSY

Epileptic dogs should not be considered refractory to medication until (I) secondary causes of seizures and precipitating factors have been excluded and (2) either serum concentrations are within the target range or the dog is suffering from unacceptabel side effects. A common mistake is to add a second drug before adequate serum concentrations of the first drug are achieved. Several alternative medicaitons are available for the management of epileptic dogs that are truly refractory to phenobarbital.

The addition of potassium bromide improves seizure control in approximately 80% of dogs with epilepsy that is refractory to phenobarbital or primindone; 21% to 26% of dogs will become seizure-free. Because of its minimal effects on liver function, bromide is also indicated in epileptic dogs with liver disease. The long half-life of bromide (16.5 to 25 days) means that two to three weeks are required before bromide levels enter the target range and three to four months are required before a steady state is attained. Bromide concentrations should be measured at one and four months after initiating therapy.

Side effects of combined therapy with phenobarbital and bromide include polyuria, polydipsia, polyphagia, transient sedation, and rarely, pancreatitis. Ataxia may occur at serum concentrations of bromide greater than 1.5 mg/ml. If seizures become well controlled, the phenobarbital dose can be gradually tapered to the lowest dose that controls seizures. Some dogs can be managed with bromide alone. In fact, there is ample evidence that treatment of human epileptics with multiple drugs is usually no more effective than therapy with a single agent.

Several other drugs have been used to improve seizure control in dogs refractory to standard therapy. Specific recommendations are not feasible because the clinical usefulness, and in some cases the pharmacokinetics of these drugs have not been fully studied. Because of drug interactions, serum concentrations of each medication should be carefully monitored when administering multiple drugs. Chlorazepate valproate, or mephenytoin may improve seizure control when administered in addition to phenobarbital.

In some epileptic dogs (especially large breeds) that are appropriately managed, seizures cannot be adequately controlled without unacceptable side effects. Some owners may accept partial control if they understand that seizures of short duration are rarely life threatening. Frequent or severe seizures, especially episodes of status epilepticus, may severely compromise the dog’s quality of life and necessitate euthanasia.

As research increases our understanding of the cellular pathogenesis of seizures and mechanisms of antiepileptic drug actions, newer antiepileptic drugs are becoming available. Although,not yet routinely used in veterinary medicine, surgical therapy is indicated in human patients with certain types of medically intractable epilepsy. Improvements in imaging and electrophysiologic techniques in veterinary medicien may allow surgery to be considered for epileptic dogs refractory to medical management.

CONCLUSION

Appropriate management of epileptic dogs entails obtaining an accurate diagnosis, ensuring proper client education, selecting an appropriate antiepileptic medication, and periodic evaluation and therapeutic drug monitoring to determine a dose that controls the seizures and avoids side effects. If seizures are still poorly controlled, the use of bromide is often beneficial. By following these principles, seizures can be controlled in most dogs with idiopathic epilepsy.

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1.) Treatment of canine epilepsy may be unsuccessful if:
   b.) Clients are inadequately informed.
   c.) Precipitating factors are undetected.
   d.) An improper antiepileptic medication is chosen
   e.) All of the above

1.) Which of the flollowing is consistent with a diagnosis of idiopathic epilepsy?
   b.) Temporary ataxia and depression immediately after a seizure
   c.) Presence of focal seizures
   d.) Persistent, mild hemiparesis
   e.) Onset of seizures at seven years of age

1.) Which of the flollowing is characteristic of generalized seizure?
   b.loss of conciousness
   c.urination
   d.extensor rigidity of all limbs
   e.all of the above

1.) Which of the following statements regarding antiepileptic therapy is true?

b.) Phenobarbital is the initial drug of choice in epileptic dogs
c.) Polyruia, polydipsia and sedation are common side effects
d.) Optimum therapy requires frequent reevaluation and occasional dose adjustments
e.) All of the above

1.) Which of the following statements regarding therapeutic monitoring of serum phenobarbital concentrations is true?
b.) Serum concentrations should be evaluated approximately 24 hours after starting therapy
c.) The target range is 50 to 90 micrograms/ml
d.) The serum sample should be collected immediately before the next dose
e.) The primary goal of antiepileptic therapy is to achieve a serum concentration within the target range

1.) Which of the following statements regarding hepatotoxicity due to antiepileptic medication is true?
b.) Hepatic injury is irreversible
c.) Elevated serum alkaline phosphatase indicates morphologic liver damage
d.) Bromide should be used as an alternative therapy
e.) Phenobarbital has not been associated with severe hepatotoxicity

1.) Approximately how many dogs with idiopathic epilepsy refractory to phenobarbital will have improved seizure control with the addition of bromide therapy?
b.) 10%
c.) 50%
d.) 25%
e.) 80%

1.) Which of the following is an appropriate recommendation for a dog with idiopathic epilepsy that has poorly controlled seizures and a trough serum pehnobarbital concentration of 15 micrograms/ml.
b.) Question the owner regarding compliance, and if compliance is good, increase the dose of phenobarbital.
c.) Change therapy to potassium bromide
d.) Add chlorazepate to the treatment regimen
e.) Change therapy to valproate

1.) A dog with focal seizures, blindness in the left visual field and proprioceptive deficits on the left most likely has:
b.) idiopathic epilepsy

c. metabolic disease
d.) toxicity
e.) intracranial disease

1.) Which of the following is indicated in a previously well-controlled epileptic that suddenly suffers an increase in seizures?

b.) Question the owner about other medications the dog may have received
c.) Perform a physical and neurologic examination
d.) Evaluate serum antiepileptic drug concentration
e.) All of the above

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