

Idiopathic Epilepsy in Dogs and Cats

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KEYWORDS

• Seizures • Phenobarbital • Bromide • Treatment

Epilepsy is a group of heterogeneous conditions that share a common feature—chronic, recurring seizures. The terms epilepsy and seizures are not synonymous. A seizure is the clinical manifestation of abnormal electrical activity in the brain.¹ It is a specific event in time. Epilepsy refers to multiple seizures occurring over a long period of time. Although there is no universal agreement on the minimum number of seizures or period of time, a useful clinical definition is two or more seizures over a month or more. Not all seizures are associated with epilepsy. For example, a seizure can be the reaction of a normal brain to a transient insult, such as intoxication or metabolic disorder. This is called a provoked seizure or reactive seizure.^{1,2} If seizures stop when the underlying condition resolves, the patient does not have epilepsy, because the condition is not chronic. On the other hand, if a patient has several seizures over a period of a month or more, and there is no detectable short-term illness responsible for the seizures, then we would say the patient has the condition called epilepsy.

Because there are many causes of chronic recurrent seizures, epilepsy is not a specific disease but rather a diverse category of disorders. Epilepsy is broadly divided into idiopathic and symptomatic disorders. Symptomatic epilepsy, also called secondary epilepsy, is when the seizures are caused by an identifiable structural lesion of the brain, such as a tumor.^{1,3} Idiopathic epilepsy, also called primary epilepsy, is chronic recurring seizures with no underlying structural brain lesion or other neurological signs.^{1,3} Here, the term “idiopathic” means a disorder “by itself” not “cause unknown.” The term idiopathic epilepsy is not applied simply to any patient in whom the cause of the seizures is unknown. Instead, it refers to recognized clinical syndromes with typical clinical features, such as age of onset and lack of other neurological abnormalities. The term “essential” is often used to convey the same meaning, as in essential hypertension.

Several other terms are commonly used. The ictus is the seizure itself. Postictal signs are transient clinical abnormalities in brain function that are caused by the ictus and appear when the ictus has ended. Postictal signs typically last a few minutes to hours and can include confusion, blindness, ataxia, and deep sleep.^{4–6} In most cases,

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vomiting, diarrhea, and apparent abdominal pain.¹² A syndrome characterized by drooling, retching, dysphagia, and painful enlargement of the mandibular salivary glands is likely a form of focal autonomic seizures.^{13,14} Complex focal seizures (formerly called psychomotor seizures) are focal seizures with alterations of awareness. Affected patients may not respond to their owner and often engage in automatisms, which are coordinated, repetitive motor activities such as head pressing, vocalizing, or aimless walking or running.⁴ Some complex focal seizures are manifested as impaired consciousness and bizarre behavior, such as unprovoked aggression or extreme, irrational fear.^{15,16} A secondarily generalized seizure usually begins with a focal seizure that evolves into a generalized tonic-clonic seizure. The secondary spread can occur so rapidly that the initial focal component is missed and the seizure is misclassified as a generalized-onset seizure. But with close observation, including videotape review of the seizures, it is apparent that secondarily generalized seizures are common in dogs and cats.^{4,7,8}

CLINICAL FEATURES OF IDIOPATHIC EPILEPSY

Most dogs with idiopathic epilepsy suffer their first seizure between 1 and 5 years of age, although seizures occasionally start before 6 months or as late as 10 years of age.^{2,4,7,8} Any breed, including mix-breed dogs can be affected. Based on pedigree analysis, a genetic basis for idiopathic epilepsy is suspected in a number of breeds, including the beagle, Belgian tervuren, Keeshond, dachshund, British Alsatian, Labrador retriever, golden retriever, Shetland sheepdog, Irish wolfhound, Vizsla, Bernese mountain dog, and English springer spaniel.^{5,17-26} Genetic factors are likely in other affected breeds as well, even though genetic studies have not been published.

In the past, generalized tonic-clonic seizures were considered the most common type of seizure in dogs with idiopathic epilepsy, and some authors even claimed focal-onset seizures were inconstant with a diagnosis of idiopathic epilepsy. However, more recent observations reveal this is clearly not the case and dogs with idiopathic epilepsy can have a variety of focal-onset seizures, including secondarily generalized seizures, and some individuals have more than one type of seizure.^{5-8,25} The frequency of seizures varies tremendously, ranging from several a day to less than one a year.^{2,7} Seizures are most common during rest or sleep.⁶ Even though most seizures appear to occur spontaneously, they may be precipitated by a variety of factors. In human patients, sleep deprivation, emotional stress, menstruation, missed medication, and concurrent illness are recognized.²⁷ Similar factors are likely important in precipitating seizures in some animals.

Reflex seizures are seizures that can be provoked by specific stimuli or events.²⁸ The most common trigger in people is flickering light, usually from a television. Other triggers include immersion in hot water, reading, certain sounds, and eating. With reflex seizures, the trigger is specific and the latency between the trigger and seizure is short (seconds to minutes).²⁸ I have evaluated several dogs that suffered seizures consistently associated with sounds (lawnmower engine), automobile rides, or veterinary offices.

Idiopathic epilepsy is much less common in cats, compared to dogs, so we have less data for feline epilepsy. A genetic basis for seizures has not been documented in cats and feline epilepsy is more likely to be symptomatic than idiopathic, compared to dogs. However, idiopathic epilepsy does occur in cats. In one study, most cats with idiopathic epilepsy had their first seizure between about 1 and 5 years of age.²⁹

Table 1
Disorders that can be mistaken for seizures

Disorder	Timing of Episode	Description	Other Findings
Syncope	Exercise, excitement, or cough	Brief collapse with loss of consciousness, no or only mild abnormal movements, no postictal abnormalities	Evidence of heart disease, arrhythmia
Cataplexy/narcolepsy	Excitement such as play or food	Brief collapse with absent muscle tone	Induce attack with food
Neck pain	Movement or activity	Crying, cervical rigidity and tremor, no loss of consciousness	Pain on neck palpation/manipulation
Vestibular dysfunction	Variable	Ataxia, abnormal nystagmus, disorientation, no loss of consciousness	Positional nystagmus or other signs of vestibular disease
Metabolic encephalopathy	May be post prandial	Abnormal behavior, depression, ataxia usually lasting an hour or more	Elevated bile acids or other laboratory abnormalities
Idiopathic head tremor	Spontaneous	Head tremor with no loss of consciousness, otherwise normal gait and behavior, lasting several minutes	Most common in English bulldogs, Doberman pinschers, boxers, and Labrador retrievers
Generalized tremor syndromes	Spontaneous	Generalized tremor with no loss of consciousness or autonomic signs	Steroid-responsive tremor syndrome is most common in young, small-breed dogs; history of exposure to mycotoxin (moldy dairy products), metaldehyde, or insecticide
Exercise-induced weakness	Exercise	Short-strided gait, kyphosis, tremor, collapse, no loss of consciousness	Induced attack with exercise
Compulsive disorders, stereotypy	Situations of anxiety, conflict, or frustration	Pacing, circling/spinning, rhythmic barking, chasing real or imaginary objects, licking, chewing, hair pulling, no loss of consciousness	Detailed behavior history may identify triggering situations
Feline estrus behavior	Associated with estrus	Howling, rolling, treading with pelvic limbs, lordosis	Intact female
Myoclonus	Episodic or continuous	Sudden, shocklike contraction of a single muscle or muscle group, may be rhythmic	May persist with sleep or anesthesia

Choice of Drug

The choice of treatment depends on efficacy, safety, and price. Based on clinical experience and pharmacokinetic information, phenobarbital or bromide is the initial drug of choice for dogs with idiopathic epilepsy. They are both relatively safe, effective, and inexpensive and most veterinarians are familiar with their use. The most significant disadvantages are the side effects: sedation, ataxia, polyuria/polydipsia, and polyphagia. Levetiracetam or zonisamide is a good choice for initial therapy when the client wants to minimize side effects. Primidone is also effective but is less commonly used because of concerns it may be more likely to cause liver disease, compared to phenobarbital, although this is not well documented.^{31,32} Because of their short durations of effect in dogs, phenytoin, valproic acid, and benzodiazepines are less suitable as single agents for the control of canine epilepsy.^{33,34} In cats, phenobarbital is the initial drug of choice.

It is better to use a single drug rather than a combination of drugs for initial therapy. Disadvantages of using multiple agents include increased cost, the need to monitor and interpret serum concentrations of multiple drugs, potential drug interactions, and more complicated dosing schedules. Nonetheless, some patients do better on a combination of drugs than on a single agent. If the first drug is ineffective because of poor seizure control or side effects, then a second drug is added. If seizures become well controlled, the first drug is tapered. If this is unsuccessful, a combination of drugs may provide optimal control.

Dose

Because of the variability in absorption, distribution, and speed of metabolism among patients, published dose recommendations serve as a general guide only. Because of sensitivity to side effects and lack of prior metabolic induction, most new patients are started at the lower end of the dose range. If necessary, the dose is slowly titrated upward until seizures are controlled or the maximum tolerated dose is reached. On the other hand, patients with frequent or severe seizures are often best managed by starting at the higher end of the dose range or using a loading dose. Once the seizures are controlled, the dose may need to be adjusted downward to minimize side effects.

Pharmacokinetic Considerations

When a drug is introduced at a constant daily dose, serum concentrations will initially be low, the amount eliminated per day will be smaller than the daily dose, and drug concentrations will increase. As concentration increases, so does elimination until it equals the daily maintenance dose (steady state). The time to reach steady state depends on the elimination half-life of the particular drug; 87% of steady-state concentrations occur at three half-lives and 97% occur at five half-lives.³⁴ In the case of drugs that are eliminated slowly, the time to reach steady state may be several weeks (phenobarbital) or months (bromide). When adequate serum concentrations are needed sooner, a loading dose can be administered. Simplistically, the loading dose is the sum of all the daily doses that would have been administered before steady state, minus the amount of drug that would have been eliminated during this period.³⁴ The major limitation of a loading dose is there is no time for tolerance to the sedative side effects to occur, so side effects are more common compared with gradual increases in drug concentrations.³⁴

The pharmacokinetics of certain drugs may change over time. For example, chronic administration of phenobarbital is associated with hepatic enzyme induction that

recurrence, which is most likely during withdrawal or within several months of stopping therapy. If seizures recur, retreatment usually regains seizure control.

ANTISEIZURE DRUGS

Phenobarbital

Phenobarbital prolongs opening of the chloride channel at the GABA_A receptor.⁴⁰ Phenobarbital is effective in 60% to 80% of dogs with idiopathic epilepsy if serum concentrations are maintained within the target range.^{32,33,37} Many clients are willing to maintain epileptic dogs on phenobarbital therapy for a long period of time and feel their pet still has a high quality of life.⁴¹ The initial dose is 2 to 3 mg/kg every 12 hours, but autoinduction usually necessitates subsequent increases in dose to maintain a trough serum concentration of 20 to 35 µg/mL. In some patients, autoinduction may eventually shorten the half-life to 36 hours or less and an 8-hour dosing interval is indicated to minimize fluctuation of serum levels.³⁴ Measurement of both a peak and trough level allows estimation of half-life and is helpful in determining the need for more frequent dosing.³⁴

The main limitation of phenobarbital is its propensity to cause sedation. This is most prominent during the first few weeks after starting therapy or increasing the dose. Hyperexcitability and restlessness can occur, especially during the first few weeks of therapy. Polyuria, polydipsia, and polyphagia are the most common long-term side effects. The most common laboratory changes are mild to moderate elevations of serum alkaline phosphatase and other hepatic enzymes. These changes do not necessarily indicate clinically significant liver disease. Serious liver toxicity is less common and may be more likely with serum concentrations above 35 µg/mL.⁴² Clinical signs of hepatotoxicity include anorexia, sedation, ataxia, icterus, and ascites. Laboratory evidence includes proportionally larger increases of alanine transaminase activity compared to alkaline phosphatase activity, elevations in bile acids, and an increase in serum phenobarbital concentrations despite no increase in dose.⁴² Monitoring serum bile acids every 6 months should be considered to screen for liver disease in dogs on long-term phenobarbital therapy. Hepatotoxicity may be reversible if it is detected early and the phenobarbital is withdrawn. However, this adverse effect can be irreversible and ultimately fatal.⁴² Polytherapy with phenobarbital and other potentially hepatotoxic drugs, such as phenytoin and primidone, may increase the risk of hepatotoxicity and should be avoided if possible.⁴² Hematologic abnormalities, including neutropenia, anemia, and thrombocytopenia are rare adverse effects and may represent an idiosyncratic reaction rather than a dose-related effect.⁴³ These changes are reversible with withdrawal of the drug.

Cats tolerate phenobarbital well, although sedation, polyuria, polydipsia, and polyphagia are possible. The risk of hepatotoxicity seems to be minimal in cats and liver enzyme induction is much less prominent than in dogs.⁴⁴ Dosing and therapeutic monitoring are similar to those for dogs.

Bromide

Bromide is effective as initial therapy in dogs and as add-on therapy when phenobarbital does not provide adequate seizure control.^{45,46} Bromide is freely filtered by the glomerulus and reabsorbed by the kidneys in competition with chloride. Because of this extensive reabsorption, the elimination half-life in dogs is slow, 21 to 24 days, and steady-state concentrations are achieved at 2.5 to 3.0 months.

Bromide is usually administered as potassium bromide or sodium bromide in solution, capsules, or tablets. Small dose adjustments are easier when using the liquid.

inappropriate behavior, ataxia, paraparesis, tetraparesis with normal or decreased spinal cord reflexes, dysphagia, and megaesophagus.⁵⁴ Mild cases of bromism are treated with dose reduction. More severe cases are managed by temporarily stopping the bromide, diuresis with intravenous saline, and furosemide. A lower dose of bromide is started once the signs of toxicity resolve.⁵⁴

Bromide is not safe in cats because of the risk of inducing pneumonitis. This is reversible by stopping the drug but it can be life threatening.^{55,56}

Zonisamide

Zonisamide is a sulfonamide derivative that is chemically distinct from other commonly used antiseizure drugs. It blocks voltage-dependent sodium channels, as well as T-type calcium channels.⁴⁰ Zonisamide is metabolized by hepatic microsomal enzymes and has an elimination half-life of approximately 15 hours in dogs, with steady state levels achieved in 3 to 4 days.^{57,58} The drug is well tolerated with transient sedation the most common side effect. Adding zonisamide improves seizure control in 80% to 90% of dogs with seizures poorly controlled by other drugs.^{59,60} Based on clinical experience, zonisamide is also effective as monotherapy and is a good choice for initial therapy when the client wishes to minimize side effects associated with bromide and phenobarbital. Zonisamide has no effect on liver enzymes but its elimination half-life is reduced by enzyme-inducing drugs such as phenobarbital.⁵⁸ The initial dose for zonisamide monotherapy is 5 mg/kg every 12 hours. When used in combination with phenobarbital, the dose is 10 mg/kg.

The elimination half-life of zonisamide in cats is 35 hours.⁶¹ Limited clinical experience indicates 5 to 10 mg/kg once daily is an appropriate dose in cats.

Levetiracetam

Although its precise mechanism of action is unknown, levetiracetam binds to synaptic vesicle protein and has actions on GABA- and glycine-gated currents, as well as voltage-dependent potassium currents.⁴⁰ Levetiracetam is an effective antiseizure drug in dogs with minimal side effects.⁶² Approximately 70% to 90% of the administered dose is excreted unchanged in the urine; the remainder of the drug is hydrolyzed in serum and other organs. The elimination half-life in dogs is 3 to 4 hours but levetiracetam seems to exert antiseizure effects longer than suggested by its serum half-life.⁵⁰ In dogs also taking phenobarbital, the elimination half-life is shortened to about 1.7 hours.⁶³ Transient sedation is a possible but uncommon side effect.

Clinical experience indicates levetiracetam is effective as monotherapy at 20 mg/kg every 8 hours and based on its wide margin of safety this drug is also a good choice for monotherapy when clients want to minimize side effects. Levetiracetam is also effective as add-on therapy at 20 mg/kg every 8 hours.⁶² However, recent pharmacokinetic information suggests a higher dose may be optimal when using levetiracetam in conjunction with phenobarbital.⁶³ Therapeutic monitoring is available but not necessary in routine cases because the drug has a wide margin of safety and there is no clear correlation between serum concentration and clinical effects.

In cats, the elimination half-life of levetiracetam is about 3 hours.⁶⁴ At 20 mg/kg every 8 hours, the drug is effective as add-on therapy with phenobarbital in cats with poorly controlled seizures. The drug is well tolerated with mild, transient sedation and decreased appetite being uncommon side effects.⁶⁴

Gabapentin

Gabapentin binds to neuronal voltage-gated calcium channels, inhibiting calcium flow. A major advantage of this drug in people is that it is excreted unchanged by the

hepatopathy, which has severely limited the use of this drug in human patients.⁴⁰ In dogs, about 30% of the administered dose is metabolized by the liver and the rest is excreted unchanged in the urine.^{76,77} The elimination half-life in adult dogs is 5 to 6 hours.^{76,77} Felbamate is effective as add-on therapy as well as initial monotherapy in dogs.⁷⁸

A recommended starting dose is 15 mg/kg every 8 hours. The dose can be increased in 15-mg/kg increments every 2 weeks until seizures are controlled. Doses as high as 70 mg/kg every 8 hours are required and tolerated in some dogs. Therapeutic monitoring is not particularly useful because target ranges have not been well established for dogs. Potential side effects include nervousness and keratoconjunctivitis sicca.^{50,78} Mild thrombocytopenia and leucopenia have also been reported; these resolved after stopping the drug.⁷⁸ Hepatic disease has been noticed in some dogs taking felbamate in conjunction with other potentially hepatotoxic drugs, such as phenobarbital, so liver function should be monitored periodically.⁷⁹

STATUS EPILEPTICUS AND CLUSTER SEIZURES

Status epilepticus is a seizure lasting at least 5 minutes or two or more discrete seizures without full recovery of consciousness between seizures.^{80,81} Cluster seizures (serial seizures, acute repetitive seizures) are a bout of multiple seizures occurring over a short period of time that is different from the patient's typical seizure pattern.⁸² A useful clinical definition of cluster seizures is two or more seizures occurring within a 24-hour period in which the patient regains consciousness between the seizures.⁸⁰ About 50% to 60% of dogs with idiopathic epilepsy suffer cluster seizures or status epilepticus, and large-breed dogs are at increased risk.⁸¹ Status epilepticus is a medical emergency with a mortality of up to 25% in dogs.⁸³ Although most dogs with idiopathic epilepsy have a normal lifespan, survival time is about 3 years less for those with episodes of status epilepticus.⁸¹

Generalized status epilepticus can be divided into two stages. The first stage is characterized by generalized tonic-clonic seizures and an increase in autonomic activity that causes hypertension, hyperglycemia, hyperthermia, and increased cerebral blood flow. The second stage starts after about 30 minutes and is characterized by hypotension, hypoglycemia, decreased cerebral blood flow, and increased intracranial pressure. During the second stage, violent motor activity often stops despite continued abnormal electrical activity in the brain. These metabolic derangements are life threatening but even in the absence of systemic effects and obvious motor activity, the excessive electrical activity in the brain starts to cause brain damage at about 30 minutes. Experimental studies suggest that with 15 to 30 minutes of seizure activity, reverberating circuits develop within the brain and seizures become self-sustaining.⁸⁴ Therefore the focus of treatment is to stop the seizure early.

At-Home Treatment

Status epilepticus usually begins at home. Traditionally this requires the client to rapidly transport the seizing patient to a hospital, which delays treatment. Because the focus of treatment is early termination of seizures, treatment that the client administers at home is a major advantage. Rectal administration of a parenteral solution of diazepam by the client is effective in decreasing the need for emergency veterinary treatment in these patients.^{85,86} Rectal administration of diazepam results in higher and earlier peak serum concentrations compared with either oral or intramuscular routes.⁸⁵ The client administers 1 mg/kg diazepam per rectum using a

REFRACTORY EPILEPSY

In general, epilepsy is refractory when, despite appropriate drug therapy, the patient's quality of life is compromised by frequent or severe seizures or side effects of medication.⁸⁹ Precise definitions vary based on the context but there are three main components: number of antiseizure drugs used, frequency of seizures, and duration of noncontrolled epilepsy.⁹⁰ Clinically useful criteria are (1) lack of response to two antiseizure drugs, (2) at least one seizure per month, and (3) duration of at least a year.⁹⁰ Approximately 25% of dogs treated for epilepsy at referral centers are never well controlled with antiseizure drugs.^{32,33,45} In patients with apparent refractory epilepsy, it is essential to search for errors in diagnosis or management that may be responsible for treatment failure. Diagnostic errors include failure to recognize nonepileptic paroxysmal disorders and underlying causes for the seizures. These can usually be avoided by careful history taking, thorough examination, and appropriate use of ancillary diagnostic tests, such as neuroimaging and CSF analysis. Errors in drug therapy include the use of ineffective drugs, incorrect dosing, and poor compliance. Approximately 30% to 50% of human patients with epilepsy do not comply with their prescribed therapy.⁹⁰ Similar data have not been published for our patients but compliance is probably a similar problem in veterinary medicine. A common cause for poor control is the use of several drugs that were not given for long enough or at high enough doses. Therapeutic monitoring is helpful in identifying low blood concentrations caused by insufficient dose or poor compliance. Referral to a neurologist should be considered if control is not achieved within a reasonable period of time or if the diagnosis is uncertain.

SUMMARY

The following principles are important in the management of idiopathic epilepsy. The diagnosis must be accurate and correctable underlying conditions must be excluded. The client is counseled about the implications of the diagnosis and treatment. The dose of antiseizure medication is individualized for the patient, considering degree of seizure control, side effects, and measurements of serum concentrations. A second drug should be substituted for the first drug before a combination of drugs is used. Alternative treatments should be considered if seizures remain uncontrolled despite appropriate drug therapy. Good communication with the client and clear and sympathetic explanation of the proposed treatment is essential. Treatment is successful in most cases, allowing the pet and client to enjoy a good quality of life.

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