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. 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. 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. Idiopathic epilepsy, also called primary epilepsy, is chronic recurring seizures with no underlying structural brain lesion or other neurological signs. 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. In most cases,
the ictus lasts only a few minutes. Some patients with seizures experience a prodrome, which is long-lasting abnormality occurring hours to days before a before a seizure, such as restlessness or anxiety.\textsuperscript{4,5,7,8} An aura is a subjective sensation at the start of a seizure before there are observable signs.\textsuperscript{4,9} The difference between a prodrome and an aura is that prodromes are longer lasting and not associated with abnormal electrical activity in the brain. Human patients describe various sensations during their auras, including dizziness, tingling, and anxiety.\textsuperscript{9} Common manifestations of auras in animals are hiding, seeking the owner, agitation, or vomiting just before a seizure.\textsuperscript{4} In other cases an aura occurs alone, which constitutes a sensory seizure.

**DESCRIPTIONS OF SEIZURES**

Several classification systems have been developed for human epileptic seizures based on clinical signs, etiology, and electroencephalographic (EEG) information. Applying these schemes to veterinary patients is problematic because not all seizure types in human patients are recognized in animals and EEG data are usually not available for our patients. Therefore, the following descriptive list is offered not as a formal classification but to facilitate communication among clinicians.

**Generalized-onset Seizures**

Generalized-onset seizures are those in which the first clinical signs indicate initial involvement of both cerebral hemispheres. Consciousness may be impaired and motor manifestations are bilateral. The most common type of generalized seizure is a generalized tonic-clonic seizure (formerly called grand mal seizures). The first part of the seizure is the tonic phase, during which there is sustained contraction of all muscles. The animal typically loses consciousness and falls to its side in opisthotonus with the limbs extended. Respirations are often irregular or absent and cyanosis is common. Autonomic signs such as salivation, urination, and defecation are common. The tonic phase lasts for a minute or so and then gives way to the clonic phase, during which there is rhythmic contraction of muscles, manifested as paddling or jerking of the limbs and chewing movements. Some animals suffer milder generalized tonic-clonic seizures in which consciousness is maintained.\textsuperscript{7,8}

Another type of generalized seizure is a tonic seizure, in which motor activity consists only of generalized muscle rigidity without a clonic phase.\textsuperscript{7,8} Less common are clonic seizures, in which there is no tonic component; atonic seizures, which consist of a sudden, often brief loss of postural tone causing the patient to fall or drop it’s head; and myoclonic seizures, characterized by brief, shocklike contractions that may be generalized or confined to individual muscle groups.\textsuperscript{10} There are other causes of myoclonic jerks in animals; that is, not all myoclonic jerks are seizures.

**Focal-onset Seizures**

Focal-onset seizures are those in which the initial clinical signs indicate abnormal activity in one region of a cerebral hemisphere. Focal motor seizures consist of abnormal movements of a body part, such as turning the head to one side, rhythmic contractions of a limb or facial muscles, or chewing movement.\textsuperscript{4,7} Focal sensory seizures cause abnormal sensations such as tingling, pain, or visual hallucinations. An aura that does not evolve into loss of consciousness is a focal sensory seizure. Because the sensations are subjective, it can be difficult to recognize sensory seizures in animals, but “fly-biting” seizures may be a form of sensory seizures with visual hallucinations.\textsuperscript{11} Focal autonomic seizures cause predominately autonomic signs, such as
vomiting, diarrhea, and apparent abdominal pain.\textsuperscript{12} A syndrome characterized by drooling, retching, dysphagia, and painful enlargement of the mandibular salivary glands is likely a form of focal autonomic seizures.\textsuperscript{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.\textsuperscript{4} Some complex focal seizures are manifested as impaired consciousness and bizarre behavior, such as unprovoked aggression or extreme, irrational fear.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5–8,25} The frequency of seizures varies tremendously, ranging from several a day to less than one a year.\textsuperscript{2,7} Seizures are most common during rest or sleep.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{26} 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.\textsuperscript{29}
DIAGNOSTIC EVALUATION

A detailed and accurate history is the foundation of diagnosis. The client’s description of the seizures, their frequency and duration, and the patient’s behavior between seizures are recorded. Ask about any focal signs at the start of the seizure, such as turning the head to one side or jerking of one limb. Any abnormalities before and after the seizure should be characterized. It is also important to determine if the events occur at a certain time of day or in association with situations such as feeding or exercise. Because the clinician may never see the seizure, the client’s observations are extremely important. In some cases it helps if the client videotapes the episodes.

Ask about familial history of seizures, significant injuries or illnesses, vaccination status, diet, and potential exposure to toxins. Ask about any prescription or nonprescription medications. Any interictal abnormalities are noted, such as changes in behavior, gait, appetite, weight, or sleep habits. The client is often the best person to identify subtle changes in personality or behaviors that are not readily apparent to the clinician in the examination room. Finally, it is essential that the veterinarian understand the client’s lifestyle and relationship with his or her pet. The prognosis for epilepsy depends greatly on the level of care the client is willing and able to provide and the impact of their pet’s illness on the family.

A thorough physical examination is important to detect signs of systemic illness that might suggest an underlying cause for the seizures. Perform a complete neurological examination to detect any persistent neurological deficits. Cerebral lesions often cause focal, relatively subtle deficits such as delayed proprioceptive positioning on one side or blindness in one visual field. Be careful when interpreting the examination shortly after a seizure because any generalized deficits, such as ataxia, depression, or blindness may be a result of postictal disturbances and not necessarily indicate underlying brain disease. Repeating the examination in 24 to 48 hours may be necessary to determine if any deficits persist.

A complete blood count and serum chemistry profile are indicated in any animal with one or more seizures. Blood lead determination is performed in patients with possible exposure to lead, patients from areas with a high incidence of lead poisoning, and in animals younger than 1 year of age. Serum bile acids are helpful in young animals to identify or rule out a porto-systemic shunt.

The diagnostic evaluation is designed to answer two questions: (1) is the patient having seizures, and (2) if so, what is the cause of the seizures. Seizures are recognized by their spontaneous onset, stereotypic signs, self-limiting time course, and postictal signs. Disorders that can be mistaken for seizures are listed in Table 1.

Idiopathic epilepsy is a clinical diagnosis based on the typical age of onset, lack of interictal abnormalities, and exclusion of other causes. Symptomatic epilepsy should be suspected when (1) seizures start before 1 or after 5 years of age, (2) the patient suffers focal seizures, (3) there is a sudden onset of multiple seizures, or (4) there are interictal abnormalities detected on history, examination, or laboratory tests.

Brain imaging (computed tomography or magnetic resonance imaging) and cerebrospinal fluid (CSF) analysis are indicated in patients with interictal neurologic deficits, focal seizures, seizures refractory to drug therapy, an onset of seizures at younger than 1 or older than 5 years of age, and any cat with recurring seizures. Brain imaging and CSF analysis are also appropriate when the client wants to be reassured there is not a progressive brain lesion responsible for their pet’s seizures. Many clients feel that the cost of brain imaging is worthwhile even when the results are normal because it helps the client understand the cause of his or her pet’s seizures. Imaging is ideally performed first and based on those results, CSF can be collected during the
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Timing of Episode</th>
<th>Description</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>Exercise, excitement, or cough</td>
<td>Brief collapse with loss of consciousness, no or only mild abnormal movements, no postictal abnormalities</td>
<td>Evidence of heart disease, arrhythmia</td>
</tr>
<tr>
<td>Cataplexy/narcolepsy</td>
<td>Excitement such as play or food</td>
<td>Brief collapse with absent muscle tone</td>
<td>Induce attack with food</td>
</tr>
<tr>
<td>Neck pain</td>
<td>Movement or activity</td>
<td>Crying, cervical rigidity and tremor, no loss of consciousness</td>
<td>Pain on neck palpation/manipulation</td>
</tr>
<tr>
<td>Vestibular dysfunction</td>
<td>Variable</td>
<td>Ataxia, abnormal nystagmus, disorientation, no loss of consciousness</td>
<td>Positional nystagmus or other signs of vestibular disease</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>May be post prandial</td>
<td>Abnormal behavior, depression, ataxia usually lasting an hour or more</td>
<td>Elevated bile acids or other laboratory abnormalities</td>
</tr>
<tr>
<td>Idiopathic head tremor</td>
<td>Spontaneous</td>
<td>Head tremor with no loss of consciousness, otherwise normal gait and behavior, lasting several minutes</td>
<td>Most common in English bulldogs, Doberman pinschers, boxers, and Labrador retrievers</td>
</tr>
<tr>
<td>Generalized tremor syndromes</td>
<td>Spontaneous</td>
<td>Generalized tremor with no loss of consciousness or autonomic signs</td>
<td>Steroid-responsive tremor syndrome is most common in young, small-breed dogs; history of exposure to mycotoxin (moldy dairy products), metaldehyde, or insecticide</td>
</tr>
<tr>
<td>Exercise-induced weakness</td>
<td>Exercise</td>
<td>Short-strided gait, kyphosis, tremor, collapse, no loss of consciousness</td>
<td>Induced attack with exercise</td>
</tr>
<tr>
<td>Compulsive disorders, sterotypy</td>
<td>Situations of anxiety, conflict, or frustration</td>
<td>Pacing, circling/spinning, rhythmic barking, chasing real or imaginary objects, licking, chewing, hair pulling, no loss of consciousness</td>
<td>Detailed behavior history may identify triggering situations</td>
</tr>
<tr>
<td>Feline estrus behavior</td>
<td>Associated with estrus</td>
<td>Howling, rolling, treading with pelvic limbs, lordosis</td>
<td>Intact female</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Episodic or continuous</td>
<td>Sudden, shocklike contraction of a single muscle or muscle group, may be rhythmic</td>
<td>May persist with sleep or anesthesia</td>
</tr>
</tbody>
</table>
same anesthetic episode. If CSF is abnormal, titers for infectious causes of encephalitis are in order.

**GENERAL PRINCIPLES OF DRUG THERAPY**

The ideal goal of treatment is to completely eliminate seizures and avoid side effects. But total freedom from seizures and side effects remains elusive for many patients so a more realistic goal is to reduce the frequency and severity of the seizures to a level that does not substantially compromise the quality of life for the pet and family while avoiding serious side effects. Achieving this goal requires the clinician to make decisions regarding when to initiate therapy, how to promote compliance, choose appropriate drugs and doses, monitor treatment, and terminate therapy.

**When to Start Treatment**

Patients with a single seizure, provoked seizures, or isolated seizures separated by long periods of time generally do not require daily maintenance therapy. Treatment is indicated for patients with frequent seizures, a trend toward increasing frequency or severity of seizures, any episode of unprovoked status epilepticus or clusters, or an underlying, progressive disorder responsible for the seizures. Whether early treatment of idiopathic epilepsy alters the prognosis is unknown; however, one study suggests that dogs treated early in the course of epilepsy have better long-term control of their seizures compared to dogs that are allowed to have a lot of seizures before treatment is started.7

Before starting therapy, the client must believe treatment is in their pet’s best interest and must understand the necessary commitment of time, money, and emotional dedication. If the client is not fully committed to the prescribed treatment, a good outcome is unlikely. The client and veterinarian should thoroughly discuss these factors and decide together when and if treatment should be initiated, weighing the risks and benefits of treatment versus no treatment.

**Client Education**

The key to successful treatment of epilepsy is client compliance. And the best way to promote compliance is good client education. Clients should be fully informed about the nature of the disease and its treatment. They should understand the goals of therapy and potential side effects. Mild side effects are common when first starting treatment with antiseizure drugs. These will often resolve or diminish after a few weeks of treatment. If clients understand this, they are less likely to become alarmed and prematurely stop treatment if they notice side effects.

Clients must appreciate the need for regular administration of medication. They need to know what to do if a dose is missed (in general, the missed dose is given as soon as the mistake is recognized, then the next dose is given on schedule). Maintaining an adequate supply of medication is important and clients should know how to obtain refills if medication is lost or runs out during travel. Suddenly stopping antiseizure medication may precipitate seizures and should be avoided at all costs. Having clients keep a log of the date and characteristics of each seizure and any side effects is very helpful in assessing therapy. Finally, clients must not alter treatment without the advice of the veterinarian. Some clients are tempted to alter the dose based on a short-term assessment of seizure control or side effects, but frequent dose changes are detrimental and make interpretation of therapeutic monitoring difficult.
**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. 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. 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.

The pharmacokinetics of certain drugs may change over time. For example, chronic administration of phenobarbital is associated with hepatic enzyme induction that
decreases elimination half-life.\textsuperscript{35,36} Because of this autoinduction, many patients may eventually require a dose that is much higher than the starting dose.

**Monitoring Therapy**

Any drug used should be given an adequate chance to work and should not be discarded prematurely. Commonly used antiseizure drugs often must be administered for several weeks or longer before obtaining maximum antiseizure effects. Furthermore, it may take several months or more to adequately evaluate seizure control in a patient that has seizures separated by long periods of time. A common cause of poor seizure control is failure to maximize the dose before discarding a particular drug. This may lead to the need to backtrack at a later date for a second, more aggressive trial. This can be difficult, however, because once a client is convinced a particular drug is ineffective, the client is often reluctant to agree to a second trial.

Therapeutic monitoring of serum drug concentrations can be helpful in determining the optimal dose.\textsuperscript{33,34,37} Therapeutic monitoring is indicated in several situations:

1. When steady-state is reached after starting treatment, changing dose, or immediately after a loading dose. This provides a baseline to guide further changes in dose according to clinical circumstances.
2. When seizures are not controlled despite an apparently adequate dose. This helps determine the need for dose adjustment before a second drug is added.
3. When signs of dose-related toxicity occur.
4. Every 6 to 12 months to verify that changes in pharmacokinetics have not caused blood concentrations to drift out of the intended range.

In most cases, a single trough level collected just before a dose is sufficient. If the dosing interval is more than 33\% of the drug half-life, collection of a peak level (4–5 hours after a dose) along with a trough level helps document the proximity of drug levels to the toxic and subtherapeutic concentrations.\textsuperscript{34} Peak and trough levels also allow estimation of half-life so that dosing interval can be modified if necessary.\textsuperscript{34} Fasted samples are preferred because lipemia may interfere with some laboratory measurements. Serum separator tubes should not be used because the silicone may bind the drug, resulting in artificially low measurements.\textsuperscript{38}

Published therapeutic or target ranges are only an approximation, as they are based on retrospective data from a small number of patients. Although most responders attain levels within the expected range, some do well below the lower limit whereas others obtain benefit at levels above the upper limit without toxicity. Patients are “treated” when the seizures are controlled and “toxic” when they suffer dose-related side effects, regardless of what is printed on the laboratory report, so results are always interpreted with consideration of seizure control and side effects.

**Stopping Therapy**

The decision to stop therapy must be made as carefully as the decision to start. Most human patients who are seizure-free for 2 or more years with drug therapy remain so when medication is withdrawn.\textsuperscript{39} Those with the highest probability of remaining seizure-free are those who had a short duration of epilepsy and few seizures before control and those with no structural brain lesions.\textsuperscript{39} Unfortunately, lack of information on recurrence risks in animals makes it impossible to predict which veterinary patients can be successfully weaned off medication. Nevertheless, given the potential adverse effects of long-term drug therapy, attempted withdrawal of medication is reasonable in animals that are seizure-free for 1 to 2 years. The dose is gradually tapered over a period of about 6 months. The major risk of discontinuing drug therapy is seizure
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. Phenobarbital is effective in 60% to 80% of dogs with idiopathic epilepsy if serum concentrations are maintained within the target range. 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. 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. Measurement of both a peak and trough level allows estimation of half-life and is helpful in determining the need for more frequent dosing.

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. 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. 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. 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. Hematologic abnormalities, including neutropenia, anemia, and thrombocytopenia are rare adverse effects and may represent an idiosyncratic reaction rather than a dose-related effect. 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. 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. 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.
There is no difference in efficacy for the potassium or sodium salt, although potassium bromide is preferred when sodium intake must be restricted (for example, congestive heart failure). Sodium bromide is preferred when potassium intake must be restricted (for example, hypoadrenocorticism).47

The starting dose for potassium bromide is 20 to 30 mg/kg, once daily, with food. If sodium bromide is used, the dose should be decreased by 15% (ie, 17–26 mg/kg) to account for the higher bromide content of the sodium salt.48 The dose is subsequently adjusted based on clinical effects and therapeutic monitoring. The target range of bromide is approximately 1 to 2 mg/mL when used concurrently with phenobarbital and 1 to 3 mg/mL when used as monotherapy.45,46 I generally measure concentrations at 1 month and 3 months after starting maintenance therapy; concentrations at 1 month will be approximately 50% the level at steady-state. The timing of the sample is not critical because bromide levels do not fluctuate much throughout the day.

A loading dose may be used to obtain target serum concentrations sooner, for example in patients with frequent seizures or when phenobarbital must be rapidly withdrawn because of adverse effects. There are several protocols, but I administer 400 mg/kg divided into 8 doses given over a 48-hour period; that is, 50 mg/kg every 6 hours for 2 days. Administering the entire loading dose at once will usually cause vomiting. After the loading dose is completed, maintenance dosing is started. A sample for monitoring is obtained immediately after the loading to assess results of loading and then at 1 month to evaluate the maintenance dose.

When bromide is added to phenobarbital to improve seizure control, the current phenobarbital dose is continued while maintenance dosing of bromide is started. After 3 months, if seizures are well controlled and the serum concentration of bromide is at least 1.5 mg/mL, it may be possible to taper the phenobarbital, decreasing the dose in 25% increments every 2 to 4 weeks. If seizures become more frequent as the phenobarbital is withdrawn, the patient may require polytherapy with both drugs. A similar approach is used when converting to bromide because of adverse effects from phenobarbital. However, if phenobarbital must be withdrawn quickly, a loading of bromide is administered and the phenobarbital is tapered over a 2-week period while maintenance doses of bromide are administered.

Because bromide competes with chloride for renal elimination, high chloride intake increases bromide elimination, which increases the dose requirement.49 Thus, the diet should not be changed during treatment. In dogs being fed high-chloride diets, such as some prescription diets, serum bromide concentrations should be monitored carefully.49 Renal insufficiency decreases bromide elimination, so in dogs with persistent isosthenuria or azotemia, the initial dose of bromide should be halved and serum bromide concentrations monitored closely to avoid toxicity.48

Side effects of bromide include sedation, ataxia, weakness, polyuria, polydipsia, and polyphagia.45 Less common are limb stiffness that can mimic orthopedic disease, irritability, restlessness, pruritic skin rash, and persistent cough.50 Vomiting can occur, probably because of the direct gastric irritation by the hypertonic bromide salt. Administering the drug with food, dividing the daily dose into two or more doses, and the use of sodium bromide instead of potassium bromide are helpful in preventing vomiting.34,48 Clinical experience and several laboratory studies suggest bromide alone or in combination with phenobarbital may increase the risk of pancreatitis.51–53 Many laboratory assays cannot distinguish between chloride and bromide, so bromide therapy may artifically increase serum chloride measurements.

Bromide toxicity (bromism) can develop at doses or serum concentrations near or above the upper end of the recommended ranges and is more common with inadequate therapeutic monitoring.54 Signs of bromism include stupor or coma, blindness,
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. Levetiractam 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
kidneys, is not metabolized by the liver, and has little or no potential for drug interac-
tions.40 In dogs, however, gabapentin is partially metabolized to N-methyl-gabapen-
tin, with an elimination half life of 3 to 4 hours.65 Gabapentin improves seizure
control when added to phenobarbital and/or bromide.66,67 A recommended starting
dose is 10 mg/kg every 8 hours. Mild sedation and ataxia are the most common
side effects.66,67

**Benzodiazepines**

Benzodiazepines, such as diazepam, lorazepam, clonazepam, and clorazepate, are
potent antiseizure drugs but have several characteristics that limit their use for main-
tenance therapy. Their duration of action is short, necessitating frequent administra-
tion to maintain adequate serum levels, and long-term use leads to the
development of tolerance to antiseizure activity. Tolerance has been observed in
experimental studies in dogs for diazepam, clonazepam, and clorazepate.68–70 This
may explain the clinical observation that improved seizure control is often only tempo-
rary when these drugs are used. Cross-tolerance to benzodiazepines may occur with
long-term use, rendering use of alternative benzodiazepines less effective. For
example, long-term administration of a benzodiazepine may prevent effective use of
diazepam to treat emergency seizures.47 These disadvantages have limited the use
of benzodiazepines as monotherapy for maintenance therapy; however, they are
very effective for the emergency treatment of status epilepticus or serial seizures.
They are also useful as temporary therapy when seizures can be predicted, such as
seizures precipitated by stress or sleep deprivation.

In dogs, clorazepate at 0.5 to 1.0 mg/kg every 8 hours is sometimes effective when
added to phenobarbital.34 Sustained-delivery tablets offer no advantage over regular-
release tablets in dogs.71 Clorazepate serum levels tend to decrease with time, so
subsequent dose increases are usually necessary. Because clorazepate’s half-life is
short, peak and trough levels are recommended at 2 and 4 weeks. Clorazepate often
increases phenobarbital concentrations, which can lead to side effects, so monitoring
of phenobarbital levels should also be measured at 2 and 4 weeks.34

In cats, diazepam has a longer elimination half-life than in dogs (15–20 hours vs
3–4 hours) and tolerance does not seem to be as much of a problem.44 However,
oral diazepam carries a risk of potentially fatal liver disease in cats.72,73 If used at
all, close monitoring for clinical and laboratory evidence of liver disease (alanine trans-
aminase and aspartate transaminase) is critical and the drug should be stopped at the
first sign of hepatotoxicity.

**Valproate**

Sodium valproate blocks voltage-dependent sodium channels, facilitates the effects
of the inhibitory neurotransmitter GABA, and reduces low threshold (T-type) calcium
currents.40 It is effective in human patients with all types of seizures, but use of this
drug in veterinary medicine is limited because it is metabolized fairly quickly in
dogs.74 Therefore, valproate is primarily used as polytherapy in combination with other
drugs such as phenobarbital when monotherapy is not effective.75 Potential side
effects include alopecia and hepatotoxicity. Vomiting has been reported but can
usually be prevented by administering the drug with food.75

**Felbamate**

Felbamate enhances the inhibitory effects of GABA, blocks voltage-dependent
sodium channels, and blocks the ionic channel at the N-methyl-D-aspartate
receptor.40 In people, felbamate carries a risk of aplastic anemia and fatal
hepatopathy, which has severely limited the use of this drug in human patients. In dogs, about 30% of the administered dose is metabolized by the liver and the rest is excreted unchanged in the urine. The elimination half-life in adult dogs is 5 to 6 hours. Felbamate is effective as add-on therapy as well as initial monotherapy in dogs.

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. Mild thrombocytopenia and leucopenia have also been reported: these resolved after stopping the drug. 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.

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. 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. 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. About 50% to 60% of dogs with idiopathic epilepsy suffer cluster seizures or status epilepticus, and large-breed dogs are at increased risk. Status epilepticus is a medical emergency with a mortality of up to 25% in dogs. Although most dogs with idiopathic epilepsy have a normal lifespan, survival time is about 3 years less for those with episodes of status epilepticus.

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. 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. Rectal administration of diazepam results in higher and earlier peak serum concentrations compared with either oral or intramuscular routes. The client administers 1 mg/kg diazepam per rectum using a
1-inch teat cannula or rubber catheter attached to a syringe. A dose of 2 mg/kg is recommended for dogs on chronic phenobarbital therapy, which increases benzodiazepine clearance. Treatment is administered at the first sign of a seizure and can be repeated for a total of three times within a 24-hour period. If seizures continue or the patient appears excessively depressed, the client is instructed to seek urgent veterinary care. The fact that diazepam is a controlled substance (as is phenobarbital) should not dissuade veterinarians from recommending at-home treatment with diazepam in appropriate patients. The purpose of controlled substance regulations is to minimize illegal use of these drugs, not to prevent their beneficial use in patients that need such therapy. Some pharmacists can compound diazepam suppositories, and a gel formulation of diazepam (Diastat) for rectal administration has recently become available for rectal administration in human patients. However, the absorption of these products has not been studied in dogs.

In-Hospital Management

Initial management of status epilepticus and clusters involves the basic principles of life support and drug administration to stop the seizure. Oral or nasal administration of oxygen is usually sufficient in patients with an adequate airway. Prolonged seizures and sedating antiseizure drugs often lead to loss of pharyngeal tone and risk of aspiration. These patients require intubation and ventilatory support. Adequate intravenous access is obtained as soon as possible and blood collected for glucose measurement and therapeutic monitoring in patients already on antiseizure drug therapy. Temperature, pulse oximetry, EKG, and blood pressure are monitored and any abnormalities, such as hyperthermia, are treated.

Diazepam reaches brain concentrations quickly and is an excellent choice for initial therapy of status epilepticus. The dose is 0.5 mg/kg intravenously (IV). This is repeated every 2 minutes if necessary to stop the seizure, up to a total of three doses. Rectal administration (1–2 mg/kg) works well if intravenous access is not available. Intramuscular administration is not recommended because of unpredictable absorption and pain on injection. Because of its high lipid solubility, diazepam redistributes quickly to body fat so the antiseizure effects last only 15 to 20 minutes. Therefore, it’s common for seizures to recur within 30 minutes of diazepam administration. If seizures recur after diazepam boluses, diazepam can be administered as a continuous rate infusion at 0.5 mg/kg/h, with the dose titrated based on seizure control and sedation.

Lorazepam has emerged as the preferred treatment for status epilepticus in humans because the effects last longer. Based on pharmacokinetic data, 0.2 mg/kg IV is an appropriate dose in dogs. In my clinical experience, the antiseizure effects in dogs do not last nearly as long as the 6 to 12 hours reported for people. Midazolam is an imidazobenzodiazepine that is water soluble at pH 4, so it is effective via various routes of administration. At physiological pH, the drug becomes fat soluble allowing for rapid penetration into the brain. A recommended dose range for dogs and cats is 0.07 to 0.20 mg/kg IV or intramuscularly (IM). Like diazepam, the effects of midazolam are short-lived, so a continuous rate infusion at 0.05 to 0.50 mg/kg/h can be helpful if seizures recur.

Once the seizure is stopped, it is often helpful to administer a longer-lasting drug to prevent further seizures. For patients not already on maintenance phenobarbital therapy, a loading dose of phenobarbital can be administered at 15 mg/kg slow IV or IM. An alternative protocol is to administer 3 to 6 mg/kg IV or IM every 15 to 30 minutes to attain the desired serum concentration; the serum level increases by approximately 5 μg/mL for every dose of 3 mg/kg.
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. 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. 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. Approximately 25% of dogs treated for epilepsy at referral centers are never well controlled with antiseizure drugs. 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. 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.

REFERENCES


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