Update
Seizure Management in Small Animal Practice

Karen R. Muñana, DVM, MS

KEYWORDS

• Epilepsy • Antiepileptic drug • Pharmacology • Dog • Cat

KEY POINTS

- Seizures are the most common neurologic condition encountered in small animal practice and arise from an imbalance of excitatory and inhibitory mechanisms in the brain.
- Epilepsy refers to recurrent seizures of any cause. Successful management of epilepsy requires knowledge of the pharmacologic properties of available antiepileptic medications, regular patient evaluations to assess response to therapy and monitor for adverse effects, and thorough client education to ensure that goals and expectations of therapy are understood.
- Conventional antiepileptic medications used in dogs and cats include phenobarbital and bromide. These drugs are efficacious but have a narrow therapeutic range such that side effects are common.
- Novel antiepileptic drugs used in dogs and cats include gabapentin, zonisamide, levetiracetam, and pregabalin. These drugs tend to have a wide therapeutic range, but little is currently known about their efficacy in dogs and cats.
- The successful management of an epileptic dog should include recommendations for emergency care of seizures at home. This typically consists of administration of a benzodiazepine if prolonged or repetitive seizures occur and can also include pulse therapy with an oral antiepileptic drug.

Seizures are the most common neurologic condition encountered in small animal practice, with an estimated prevalence in a referral hospital population of 1% to 2% in dogs[1,2] and 0.5% to 3.5% in cats.[1–3] Seizures are transient paroxysmal disturbances in brain function that result from an imbalance between excitatory and inhibitory neurotransmission in the brain. The resulting neuronal excitation can be identified by characteristic epileptiform activity on electroencephalography and is typically accompanied by clinical manifestations. These clinical manifestations can be expressed as alterations of consciousness, behavioral changes, involuntary motor activity, and autonomic discharge, resulting in salivation, urination, and defecation.

Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1060 William Moore Drive, Raleigh, NC 27607, USA
E-mail address: karen_munana@ncsu.edu

Vet Clin Small Anim 43 (2013) 1127–1147
http://dx.doi.org/10.1016/j.cvsm.2013.04.008 **vetsmall.theclinics.com**
0195-5616/13/$ – see front matter © 2013 Elsevier Inc. All rights reserved.

PATHOPHYSIOLOGY

Seizure activity is characterized at the neuronal level by 2 primary features, hyperexcitability and hypersynchrony. A hyperexcitable state can result from 4 general mechanisms[4]: (1) derangements of cellular metabolism that lead to excessive depolarization of the neuronal membrane (eg, failure of the Na+/K+-ATPase pump or changes in voltage gated ion channels); (2) decrease in inhibitory neurotransmission, such as that mediated by γ-aminobutyric acid (GABA); (3) increase in excitatory neurotransmission, such as that mediated by glutamate; and (4) alteration of local ion concentrations that favor membrane depolarization. Electrical fields created by neuronal activation can increase the excitability of neighboring neurons via nonsynaptic (ephactic) interactions and through the activation of recurrent excitatory collateral fibers, contributing to a hypersynchronous state.

EPILEPSY CLASSIFICATION

Epilepsy is a general term that refers to a clinical disorder characterized by recurrent seizures of any cause. In order to better characterize this diverse group of disorders, epilepsy is further classified with respect to cause. The International League Against Epilepsy has recently revised its classification scheme for human epilepsy (**Table 1**).[5] Universally accepted epilepsy terminology does not exist in veterinary medicine, although the classification scheme has generally followed International League Against Epilepsy guidelines. The terms, *idiopathic epilepsy*, *reactive epilepsy*, *symptomatic epilepsy*, and *probable symptomatic epilepsy*, are most commonly used (see **Table 1**). Idiopathic epilepsy typically has an age on onset in dogs of 1 to 5 years, although dogs outside of this age range have been described. There is evidence to support a heritable basis for disease in the Australian shepherd,[6] beagle,[7] Belgian Tervuren,[8] Bernese mountain dog,[9] border collie,[10] dachshund,[11] dalmatian,[12] English springer spaniel,[13] German shepherd,[14] golden retriever,[15] Irish wolfhound,[16] keeshond,[17] Labrador retriever,[18] lagotto Romagnolo,[19] Shetland sheepdog,[20] standard poodle,[21] and vizsla.[22]

Table 1
Epilepsy classification schemes commonly used in human and veterinary medicine

Human Epilepsy Classification	Definition	Analogous Veterinary Classification
Genetic epilepsy	Chronic recurring seizures for which there is no underlying cause other than a presumed genetic predisposition	Idiopathic epilepsy
Metabolic epilepsy	Distinct metabolic condition or disease demonstrated to be associated with an increased risk of developing seizures	Reactive epilepsy
Structural epilepsy	Congenital or acquired structural lesion in the brain associated with an increased risk of developing seizures	Symptomatic epilepsy
Epilepsy of unknown cause	Nature of underlying cause is as yet unknown	Probable symptomatic epilepsy Cryptogenic epilepsy

GENERAL PRINCIPLES OF THERAPY

Initiating Treatment

Dogs with symptomatic epilepsy should have treatment directed at the underlying cause, if possible. This is particularly important if a metabolic cause is identified, because reactive seizures are often refractory to antiepileptic drug treatment if the primary cause is not addressed.

Common guidelines exist as to when to initiate antiepileptic drug therapy. Clinicians must also take into consideration, however, the general health of the patient as well as the owner's lifestyle, financial limitations, and comfort with the proposed therapeutic regimen. A final decision should be made on a case-by-case basis with these factors in mind. As a general rule, the author recommends initiation of treatment when any of the following criteria is present:

- Seizure frequency is $\geq$1 a month.
- There is a history of cluster seizures or status epilepticus.
- The seizure itself or the postictal signs are considered especially severe.
- The owner has a strong desire to treat the seizures regardless of the frequency or severity.

Therapeutic recommendations have been based on the belief that long-term seizure management is most successful when antiepileptic therapy is initiated early in the course of disease. An epidemiologic study of Labrador retrievers with epilepsy demonstrated that dogs with a low total number of seizures prior to treatment responded better to antiepileptic therapy than dogs that had multiple seizures before treatment was initiated.[23] Similarly, among humans with epilepsy, patients with the greatest number of seizures prior to initiation of treatment are more likely to respond poorly to antiepileptic therapy.[24] Historically, this phenomenon has been attributed to kindling, in which seizure activity leads to intensification of subsequent seizures. There is little clinical evidence, however, to substantiate that kindling plays a role in either dogs[25] or humans[26] with recurrent seizures. Rather, recent epidemiologic data suggest that there are differences in the inherent severity of epilepsy among individuals, and these differences influence a patient's response to medication and long-term outcome.[27] Breed-related differences in epilepsy severity have been described in dogs, with a moderate to severe clinical course reported in Australian shepherds[6] and border collies,[10] whereas a less severe form of disease has been described in collies.[28]

Client Education

Client education is key to the successful management of epilepsy. Pet owners should have a thorough understanding of the goals and expectations of treatment prior to initiating therapy. Key points that should be discussed with owners are outlined:

- Many animals do not become seizure-free with treatment. Rather, a realistic goal might be control of seizures to an acceptable level that allows for the best quality of life.
- Antiepileptic drug therapy is lifelong in most instances.
- Managing a pet with epilepsy requires a time commitment. A lifestyle adjustment might be needed to assure that a pet receives medication at the prescribed interval each day, because even 1 missed dosage of medication can precipitate seizures in some individuals.
- There is a considerable financial commitment involved in managing a pet with epilepsy. In addition to the cost of medication, pets should have a physical

examination and laboratory evaluation performed at minimum on an annual basis.
- Antiepileptic drugs are not without side effects, and a reduction of seizures must be balanced with minimizing drug-related adverse effects.
- Owners must be committed to the treatment at the onset of therapy. Otherwise, client compliance might become a problem and treatment is less likely to be successful.

Choosing an Antiepileptic Drug

Factors to consider when choosing an antiepileptic medication include

- Mechanism of action
- Efficacy
- Adverse effects of the medication
- Potential for drug interactions
- Frequency of administration (which might influence compliance)
- Cost

Regardless of the drug used, optimal treatment results are best achieved by adopting a systematic approach to seizure management (**Fig. 1**). In general, administration of a single antiepileptic drug rather than a combination of drugs is preferred at the onset of treatment, because this avoids drug-drug interactions and provides a simpler regimen that may improve compliance.[29] Adequate treatment response is assessed based on seizure frequency once the drug has reached steady-state concentrations, serum drug concentrations when applicable, and the severity of side effects. If seizures remain inadequately controlled in an animal with serum drug concentrations within the low therapeutic range and no evidence of medication-related side effects, the dosage of the drug should be increased. A drug should not be considered to have failed until maximum dosage or therapeutic serum concentrations have been attained, or unacceptable side effects occur. If the single agent does not adequately control seizures at optimal dosages, then a second drug should be added and attempts made to gradually wean the first drug. If this is unsuccessful, polytherapy should be maintained. When choosing an add-on drug, it is preferred to use drugs with differing mechanisms of action that can be administered concurrently without the potential for drug interactions.

Assessing Safety and Efficacy

A fundamental tenet of evidence-based medicine is that the practice of medicine should be based on valid, clinically relevant research data. Guidelines for use of antiepileptic drugs in human medicine are routinely based on randomized controlled studies. In contrast, most of the data available on efficacy and safety of antiepileptic therapy in veterinary medicine are derived from retrospective or open-label studies. An analysis of 3 randomized controlled trials involving dogs with canine epilepsy demonstrated that 30% of dogs experienced a 50% or greater reduction in seizures with placebo administration.[30] Retrospective studies and open-label trials cannot account for a placebo effect and, consequently, it is likely that the efficacy data from such studies are overstated.

Monitoring Response to Therapy

Epilepsy is a chronic disease, and clinicians should view its management as such. Ideally, the goal of therapy is seizure remission; however, this cannot be achieved in most instances. Less than half of all epileptic dogs are able to maintain a seizure-free status without experiencing adverse effects from the medication.[31]

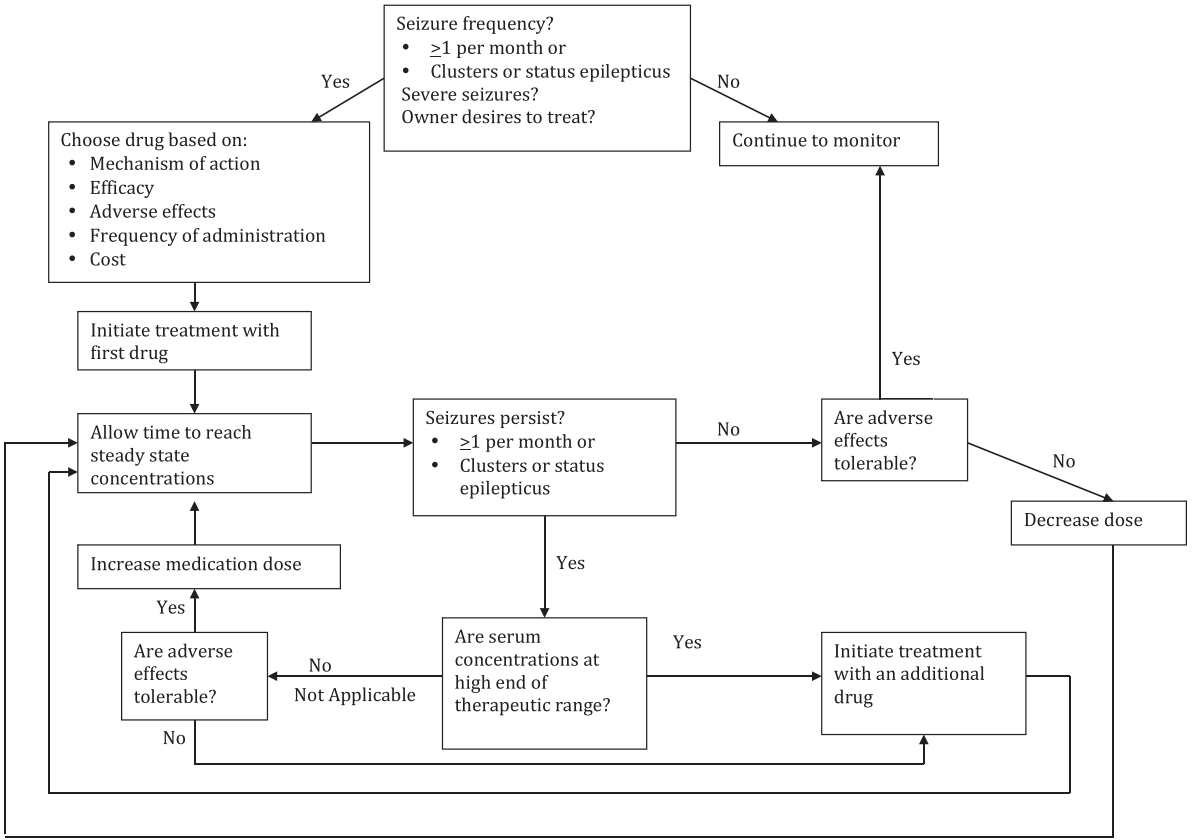

Fig. 1. Algorithm outlining the approach to the use of antiepileptic drugs in dogs and cats.

Consequently, the primary aim of treatment is to optimize control of seizures while minimizing the adverse effects of the antiepileptic medication.

Epilepsy management depends to a large extent on accurate owner observation, particularly when assessing the efficacy of therapy. Owners should be instructed to maintain a diary to keep a record of seizures that occur. The diary is also a useful place for the owner to record whether any doses of medication are not administered as scheduled and note any observed adverse effects.

Therapeutic drug monitoring is an important tool in evaluating both the efficacy and toxicity of antiepileptic medication. This is particularly important in drugs, such as phenobarbital and potassium bromide, that have a narrow therapeutic index, for which a therapeutic range has been established and levels are routinely monitored. In such instances, drug concentrations should be measured at the following times:

- After initiating treatment, once steady-state concentrations are achieved
- After each dosage adjustment, once steady-state concentrations are achieved
- When seizured are not adequately controlled
- When there is concern about possible drug-related toxicity
- At 6- to 12-month intervals to screen for any changes in drug disposition over time

It is important to have a regular assessment of serum drug concentrations even at times when seizures are well controlled, because this can be used as a basis for any changes in therapy that might be warranted in the future.

Many of the newer antiepileptic drugs developed for the treatment of humans are now used in veterinary patients. Medications, such as gabapentin, pregabalin, zonisamide, and levetiracetam, tend to have a wide therapeutic index, and serum monitoring is not routinely performed in human medicine. Although therapeutic ranges have not been established for dogs or cats, the author thinks that measurement of serum concentrations can be useful in certain instances to assess the efficacy of a given medication.

The question frequently arises as to when antiepileptic medication can be discontinued in an animal that is seizure-free. Recent research suggests that the remission rate of epilepsy in dogs, defined as freedom from seizures for a minimum of 1 year, ranges from 15% to 18%.[10,32] This remission rate includes dogs in which the seizure-free status is due to effective medical therapy as well as dogs that experience remission without treatment or a resolution of the seizure disorder. The author only considers weaning medication if an animal has experienced no seizures for a year or longer, particularly if serum drug concentrations are subtherapeutic or on the low end of the therapeutic range. This must be done slowly because an abrupt termination of antiepileptic medication can result in status epilepticus. The author reduces the dosage of medication by approximately 25% and maintains it at this level for at least the time required to reach steady-state concentrations before reducing the medication further.

PHARMACOLOGIC TREATMENT OPTIONS

Until recently, primary treatment options for dogs and cats with epilepsy were limited to phenobarbital and bromide. Although these conventional drugs still experience widespread use in veterinary practice, several new antiepileptic drugs have been developed for use in humans over the past 20 years that are now used in the treatment of canine and feline epilepsy. By providing additional treatment options, the availability of these novel drugs has made a tremendous impact on the management of epilepsy in dogs and cats. The optimum use of these drugs has yet to be established in

veterinary patients. Although their relative efficacy has not been determined, they tend to have a wide therapeutic index and offer the potential of minimizing adverse effects of treatment. Properties of the antiepileptic drugs used to treat dogs and cats are summarized in **Tables 2** and **3**.

Phenobarbital

Mechanism of action

The primary mechanism by which phenobarbital exerts it antiepileptic effect is potentiation of inhibition at the postsynaptic level through action on the $GABA_A$ receptor. Specifically, phenobarbital enhances receptor-mediated chloride currents by prolonging the opening of postsynaptic chloride channels, resulting in increased intracellular chloride concentration and subsequent hyperpolarization of the cell membrane.[33] At higher concentrations, phenobarbital also causes a presynaptic reduction of calcium dependent action potentials, which might also contribute to its antiepileptic effect.[34]

Table 2
Summary of pharmacologic properties of antiepileptic drugs used as maintenance therapy in dogs

Drug	Recommended Starting Oral Dose	Time to Steady-State Concentration (Days)	Route of Elimination	Reported Adverse Effects
Phenobarbital	2.5–3.0 mg/kg q 12 h	10–14	Hepatic metabolism—CYP enzyme system	Sedation, ataxia Polyphagia Polyuria/ polydipsia Hepatotoxicity Bone marrow suppression Hyperexcitability
Bromide	30 mg/kg q 24 h	100–200	Renal excretion	Sedation, ataxia Vomiting Polyuria/ polydipsia Polyphagia Pancreatitis
Gabapentin	10–20 mg/kg q 6–8 h	1	Renal excretion; portion undergoes hepatic metabolism	Sedation, ataxia
Zonisamide	5–10 mg/kg q 12 h	3–4	Hepatic metabolism—CYP enzyme system	Sedation, ataxia Loss of appetite
Levetiracetam	20 mg/kg q 8 h	1	Primarily renal excretion; some enzymatic hydrolysis	Sedation, ataxia
Pregabalin	3–4 mg/kg q 8 h	1–2	Renal excretion; portion undergoes hepatic metabolism	Sedation, ataxia

Table 3
Summary of pharmacologic properties of antiepileptic drugs used as maintenance therapy in cats

Drug	Recommended Starting Oral Dose	Time to Steady-State Concentration (Days)	Reported Adverse Effects
Phenobarbital	1.5–2.5 mg/kg q 12 h	16	Sedation, ataxia Weight gain Blood dyscrasias Facial pruritis
Bromide	30 mg/kg q 24 h	37	Bronchial asthma Sedation Polydipsia Vomiting Weight gain
Gabapentin	5–10 mg/kg q 8–12 h	Not reported	Sedation, ataxia
Zonisamide	5 mg/kg q 12–24 h	7	Sedation, ataxia Anorexia Vomiting Diarrhea
Levetiracetam	20 mg/kg q 8 h	1	Sedation Inappetance Hypersalivation
Pregabalin	1–2 mg/kg q 12 h	Not reported	Sedation, ataxia

Pharmacokinetics

Phenobarbital is well absorbed after oral administration in dogs, with a reported bioavailability of approximately 90%[35,36] and an absorption half-life of approximately 1.3 hours.[36,37] Peak plasma concentrations are reached 4 to 8 hours after oral administration.[36] The elimination half-life of phenobarbital in normal dogs has been reported to range from 37 to 74 hours after multiple oral dosing.[37]

Phenobarbital undergoes hepatic metabolism, and is a potent inducer of cytochrome P450 (CYP) enzyme activity in the liver. Autoinduction can occur, whereby phenobarbital increases its own rate of metabolism over time. After 90 days of administration of phenobarbital to normal dogs at a daily oral dose of 5.5 mg/kg, the elimination half-life was shown to decrease from approximately 89 hours to 47 hours.[38]

Pharmacokinetic studies of phenobarbital in cats have demonstrated that peak concentrations are achieved approximately 1 to 1.5 hours after oral administration,[39] with an elimination half-life ranging from 43 to 76 hours.[39,40]

A parenteral form of phenobarbital is available for intramuscular or intravenous (IV) administration. The pharmacokinetics of intramuscular phenobarbital has not been explored in either dogs or cats, but studies in humans have demonstrated a similar absorption after intramuscular administration to that observed with oral administration.[41] The intramuscular route is useful for administering maintenance therapy in hospitalized patients that are unable to take oral medication. Elimination half-life in dogs after IV phenobarbital administration is approximately 93 hours.[35]

Clinical use

Phenobarbital is still considered by many practitioners to be the first-line drug for the treatment of epilepsy in both dogs and cats, based on its efficacy, low cost, ease of administration, and reasonable time required to achieve steady-state concentrations.

Available data suggest that phenobarbital is the most effective antiepileptic drug currently used in veterinary medicine. Open-label studies have shown phenobarbital to be effective in approximately 60% to 80% of epileptic dogs when plasma concentrations are maintained within the therapeutic range of 20 μg/mL to 45 μg/mL.[42,43] Furthermore, the superior efficacy of phenobarbital was demonstrated in a randomized controlled trial comparing phenobarbital to bromide as a first-line antiepileptic drug in dogs, in which 85% of dogs administered phenobarbital became seizure-free compared with 52% of dogs administered potassium bromide.[44] The recommended initial starting oral dose, 2.5 mg/kg to 3.0 mg/kg every 12 hours, is expected to achieve steady-state serum concentrations at the low end of the therapeutic range (20–25 μg/mL) in most dogs.[38] The recommended starting oral dose in cats of 1.5 mg/kg to 2.5 mg/kg every 12 hours is lower than that in dogs, as is the targeted serum concentrations of 15 μg/mL to 30 μg/mL.[45] Because of considerable variability in the pharmacokinetics of phenobarbital among individuals, serum drug concentrations should be measured approximately 2 weeks after initiating therapy to confirm that therapeutic levels have been reached. If the seizures are controlled on the current dose of phenobarbital, the animal should be evaluated at 6- to 12-month intervals, to screen for any adverse effects of the drug and to monitor for any changes in serum concentrations that might be of clinical relevance. The latter is particularly important with phenobarbital, because autoinduction can result in decreased serum concentrations over time. If seizures are not controlled, the phenobarbital dose should be increased by approximately 25% and serum concentrations reassessed in 2 weeks. This process is repeated as long as seizure control remains poor, until serum phenobarbital concentrations reach 30 μg/mL or intolerable side effects develop.

The timing of blood collections for phenobarbital monitoring is not important in most dogs, because the change in phenobarbital concentrations through a daily dosing interval is not therapeutically relevant.[46] Measurement of peak and trough samples should be performed, however, in dogs that continue to have seizures on phenobarbital therapy, to ensure that there is not a daily fluctuation in serum drug concentrations. In some instances, 3-times daily dosing might be indicated.

Phenobarbital can be administered IV as a treatment of acute repetitive seizures, although therapeutic effects can take as long as 30 minutes to achieve, because the drug is less lipid soluble than diazepam.[47] A loading dose of 12 mg/kg to 24 mg/kg IV has been recommended to achieve therapeutic concentrations rapidly.[47] In phenobarbital-naïve dogs, the author administers an initial dose of 12 mg/kg IV, followed by 2 mg/kg to 4 mg/kg increments every 20 to 30 minutes to effect, with a maximum dose of 24 mg/kg. For dogs on maintenance phenobarbital therapy and cats, the IV drug is initially given at 2 mg/kg to 4 mg/kg increments every 20 to 30 minutes to effect.

Adverse effects

Common adverse effects of phenobarbital include polydipsia, polyphagia, polyuria, lethargy, and ataxia and are seen in approximately half of dogs within the first month of initiating therapy.[44] In most dogs, these adverse effects tend to improve, if not resolve, over the course of several months.[44] Adverse effects reported in cats include sedation, ataxia, and weight gain.[48] Other, less common adverse effects described with phenobarbital administration include hyperexcitability[44] and movement disorders[49] in dogs, facial pruritis in cats,[48] and blood dyscrasias in both dogs and cats.[48,50] The latter is a rare, but potentially serious, idiosyncratic reaction to phenobarbital, in which any of the cell lines can be affected. Reported adverse effects are all reversible with discontinuation of phenobarbital therapy.

The adverse effect that tends to be of greatest concern is the potential for hepatotoxicity. It is common for dogs administered phenobarbital to have increases in serum liver–associated enzymes, notably alkaline phosphatase (ALP) and alanine aminotransferase (ALT), with no clinical evidence of liver disease.[51,52] The significance of the liver enzyme increases remain controversial. In a study by Müller and colleagues,[53] normal dogs were administered a daily oral 5-mg/kg dose of phenobarbital for 29 weeks and serially evaluated with laboratory analyses, abdominal imaging, and liver histopathology obtained with ultrasound-guided biopsy. Significant increases in ALT and ALP were noted, although no evidence of morphologic liver damage was observed histopathologically, leading the investigators to conclude that this likely is a reflection of enzyme induction rather than hepatic injury.[53] A more recent study evaluated liver histopathology, as well as ALT and ALP activities, in liver homogenates from clinically healthy epileptic dogs that demonstrated elevations in serum liver–associated enzymes in conjunction with phenobarbital administration.[54] Compared with control dogs, phenobarbital-treated dogs did not have increased activities of ALT and ALP in liver homogenates but did demonstrate more severe and frequent histopathologic abnormalities commonly associated with liver injury. Results from this study do not support enzyme induction as the cause for increases in serum ALT and ALP activities but rather suggest that they might reflect subclinical hepatic injury.

Nonetheless, clinical evidence of liver disease is uncommon with phenobarbital administration, and any changes are reversible with discontinuation of the drug if identified early in the course of disease. To monitor for hepatic disease, laboratory analyses performed at 6- to 12-month intervals should be evaluated for dramatic increases or decreases in serum-associated liver enzymes over time as well as any increase in phenobarbital serum concentration not associated with a concomitant dosage increase. In addition, monitoring of fasting serum bile acids, aspartate aminotransaminase, and bilirubin might be useful, because these values do not seem affected by the potential enzyme-inducing effects of phenobarbital.[53] Furthermore, a serum phenobarbital concentration of 30 μg/mL to 35 μg/mL should be considered the maximum acceptable level, because dogs with serum phenobarbital concentrations greater than 40 μg/mL seem at increased risk for hepatotoxicity.[55]

Phenobarbital administration can lower serum concentrations of free T_4 and total T_4 in dogs, but this is not associated with a hypothyroid state.[56–58] Consequently, clinicians should use caution when interpreting the results of thyroid testing in dogs receiving phenobarbital, particularly if no clinical signs of hypothyroidism are present. In addition, phenobarbital alters the disposition of other drugs that undergo hepatic metabolism via the CYP system, including antiepileptic drugs, such as zonisamide[59] and diazepam.[60]

Phenobarbital has a narrow therapeutic index, although serious systemic side effects are uncommon. Routine, periodic patient monitoring enables most potential problems to be identified at an early stage. Furthermore, its established efficacy, ease of administration, and low cost offer clear advantages over other antiepileptic drugs, and phenobarbital is an important tool in the management of epilepsy in dogs and cats. A study designed to evaluate owners' perceptions regarding the care of epileptic dogs treated with phenobarbital discovered that most owners were pleased with their dog's quality of life on the medication.[61]

Bromide

Mechanism of action

Bromide is thought to exert its antiepileptic effect by hyperpolarizing the postsynaptic membrane.[62] After administration, bromide readily distributes to the extracellular

space and then traverses the GABA-gated chloride channels in the postsynaptic membrane to accumulate intracellularly. Bromide crosses cell membranes faster than chloride due to its smaller hydrated diameter. The intracellular accumulation of bromide leads to membrane hyperpolarization.

Pharmacokinetics

The bioavailability of bromide after oral administration in normal dogs is approximately 46%.[63] Bromide is not bound to plasma proteins and can freely diffuse across cell membranes.[62] The elimination half-life ranges from 25 to 46 days in dogs[64]; accordingly, it can take several months to reach steady-state concentrations. The elimination half-life in cats is approximately 11 days.[64] No hepatic metabolism occurs, and bromide is excreted unchanged by the kidneys. Bromide undergoes tubular reabsorption in competition with chloride, such that changes in dietary chloride can alter the disposition of bromide.[65] A high dietary chloride load increases the excretion of bromide and shortens its half-life, whereas a low dietary chloride content slows the excretion of bromide and prolongs the half-life.

Clinical use

The anticonvulsive properties of bromide have been known since the mid-1800s, although its use in veterinary medicine has experienced a resurgence after a report in 1986 of the concurrent use of bromide and phenobarbital to control refractory epilepsy in dogs.[1] Bromide has not been approved by the US Food and Drug Administration for use in humans or animals. The product used in veterinary medicine is compounded into a solution, capsules, or tablets from either the potassium-derived or sodium-derived analytic grade chemical.

Bromide was originally described as an add-on treatment for epileptic dogs that were poorly controlled with phenobarbital and was reported to improve seizure control in 53% to 72% of dogs.[1,66,67] More recently, bromide has gained use as a sole antiepileptic therapy in dogs, either as a first-line drug or in dogs with intolerable side effects from phenobarbital.[44,67] A randomized controlled study comparing the safety and efficacy of bromide and phenobarbital as first-line antiepileptic therapy in dogs reported 52% of dogs became seizure-free on bromide.[44]

The recommended starting dose for potassium bromide is 30 mg/kg orally every 24 hours. Higher doses of 40 mg/kg to 80 mg/kg might be needed, however, when used as a sole antiepileptic agent. Therapeutic ranges have been reported as approximately 1.0 mg/mL to 2.0 mg/mL when administered in conjunction with phenobarbital and 1.0 mg/mL to 3.0 mg/mL when administered alone.[67] Because steady-state bromide concentrations are not achieved for several months, a loading dose of bromide can be administered at the initiation of treatment to achieve therapeutic concentrations of the drug more rapidly. A oral loading dose of 400 mg/kg to 600 mg/kg is recommended; this should be divided and administered with food. For rapid loading, the dose can be administered over 24 hours, whereas more gradual loading can be accomplished over 5 days. Although therapeutic serum levels can be obtained quicker by administering a loading dose, the time to reach steady-state concentrations is not altered.

The use of bromide has also been described in cats. An oral dose of 30 mg/kg/d has been shown to successfully control seizures in approximately 50% of cats treated.[64] The incidence of side effects is high, however, and consequently the routine use of bromide is not recommended in cats.

Adverse effects

Common adverse effects of bromide in dogs include vomiting, lethargy, ataxia, polyuria, polydipsia, and polyphagia.[44] Vomiting is presumably due to gastric irritation

from the hypertonicity of the bromide salt. For this reason, it is recommended that bromide is administered with food. If vomiting persists, the daily dose can be divided into twice-daily administration, sodium bromide can be used instead of potassium bromide, or the compound can be encapsulated if the solution had been administered previously. The incidence of pancreatitis in dogs treated with a combination of phenobarbital and potassium bromide has been shown increased compared with dogs administered phenobarbital alone,[68] suggesting that bromide therapy might predispose to the development of pancreatitis. A causal relationship between the 2 has not been established, however. Efforts should be made to minimize changes in diet while on bromide therapy, because changes in dietary chloride can influence the rate of bromide excretion. If a diet change is necessary, the bromide level should be monitored closely for several months after the transition.

Signs of bromide toxicity in dogs develop in a dose-dependent manner and include alterations in consciousness, ataxia, and paresis that can be either upper motor neuron or lower motor neuron in character.[69] Clinical signs are most frequently recognized in dogs administered a total daily dose of bromide and serum bromide concentrations within the upper limit of the recommended ranges.[69] Treatment consisting of bromide dose reduction typically leads to rapid reversal of clinical signs. In severe cases, excretion of bromide can be facilitated by saline diuresis. Animals with renal impairment are at increased risk for the development of bromide toxicity and might require a reduction in initial dosage and more frequent monitoring of bromide levels.[70]

Adverse effects reported in cats include polydipsia, vomiting, weight gain, sedation, and coughing.[64] Coughing was reported in 38% of cats in one study[64] and is believed due to allergic bronchial disease. The respiratory compromise can be life-threatening and, for this reason, the use of bromide as an antiepileptic drug in cats is discouraged.

Gabapentin

Mechanism of action

The precise cellular mechanism of action of gabapentin is unclear. Despite being designed as a GABA agonist, it does not seem to act on the GABA receptor. There is evidence to suggest that much of the antiepileptic effect is due to binding to a specific modulatory protein of voltage-gated calcium channels, resulting in decreased release of excitatory neurotransmitters.[71]

Pharmacokinetics

Gabapentin is well absorbed after oral administration in dogs with maximum blood concentrations achieved within 2 hours.[72] Unlike humans and rodents, in which gabapentin is excreted unchanged in the urine, in dogs, approximately one-third of the absorbed dose undergoes liver metabolism prior to renal excretion,[72] with an elimination half-life of approximately 3 to 4 hours.[73] The pharmacokinetic properties of gabapentin in cats have not been described.

Clinical use

There are 2 published open-label trials evaluating the use of gabapentin as add-on therapy in dogs with refractory epilepsy. One study reported a positive response to therapy in 6 of 11 dogs,[74] whereas the other failed to identify a significant decrease in the number of seizures over the study period for the cohort of 17 dogs evaluated.[75] The recommended dose in dogs is 10 mg/kg to 20 mg/kg orally every 6 to 8 hours. Common side effects include sedation and ataxia. There are anecdotal reports of the use of gabapentin in epileptic cats, at a dose of 5 mg/kg to 10 mg/kg orally every 8 to 12 hours. The commercially available liquid formulation of gabapentin, which is often preferred when dosing cats and small dogs, contains xylitol (300 mg/mL).

Because of the potential for xylitol toxicity,[76] a tablet or capsule formulation of gabapentin should be preferentially used in dogs.

Zonisamide

Mechanism of action

Zonisamide is a sulfonamide drug with several pharmacologic effects that might contribute to its anticonvulsive properties. It has been demonstrated to block T-type calcium channels, inhibit voltage-gated sodium channels, enhance GABA release, and inhibit glutamate release.[77]

Pharmacokinetics

Zonisamide is well absorbed after oral administration to dogs, with a reported bioavailability of approximately 68% and maximum concentrations achieved in approximately 3 hours.[78] Elimination half-life is approximately 17 hours.[78] The majority of absorbed drug undergoes hepatic metabolism, followed by renal excretion.[78] Metabolism is believed to involve the CYP system, and concurrent administration of phenobarbital, which is a microsomal enzyme system inducer, has been shown to increase the clearance of zonisamide.[59] A pharmacokinetic study of zonisamide in cats demonstrated that maximum concentrations are achieved approximately 4 hours after oral administration, with an elimination half-life of approximately 33 hours.[79]

Clinical use

There is limited information on the efficacy of zonisamide in dogs, with 3 open-label trials published to date.[80–82] Two studies evaluated zonisamide as an add-on drug in a total of 25 dogs. Response rates of 58% to 82% were reported in these studies, with a median reduction in seizure frequency of 70% to 81%.[80,81] The third study evaluated zonisamide as monotherapy in 10 dogs, and reported a response rate of 60%.[82] The recommended starting dose in dogs is 5 mg/kg to 10 mg/kg orally every 12 hours. The high end of the dose range is needed when used in combination with phenobarbital, because concurrent phenobarbital administration increases the clearance of zonisamide.[59] Adverse effects described in dogs include sedation, ataxia, and loss of appetite.[80–82] In addition, recent reports suggest that more serious adverse effects can occur infrequently with zonisamide administration, including hepatotoxicity[83,84] and renal tubular acidosis.[85] There are anecdotal reports of the use of zonisamide in cats, with oral doses of 5 mg/kg orally every 12 to 24 hours most commonly used. A toxicity study in normal cats demonstrated, however, that a daily oral dose of 20 mg/kg resulted in adverse effects in half of the cats, including anorexia, diarrhea, vomiting, lethargy, and ataxia.[79]

Because zonisamide has a wide therapeutic index, serum concentrations are not routinely measured. A therapeutic range has not been established in either dogs or cats, although the human therapeutic range of 10 μg/mL to 40 μg/mL has been extrapolated for use in dogs.[80] The author finds it useful to measure serum concentrations when satisfactory seizure control is not obtained, to determine whether a dosage increase might be warranted.

Levetiracetam

Mechanism of action

Levetiracetam is unique among antiepileptic drugs with respect to its mechanism of action, in that it modulates the release of neurotransmitters by selective binding to the presynaptic protein SVA2.[86] The exact mechanism by which this produces its antiepileptic effect, however, is poorly understood. Levetiracetam has been shown to reduce current through voltage-gated calcium channels, inhibit release of calcium

from intraneuronal calcium stores, and inhibit burst firing of neurons, thereby suppressing hypersynchronization and propagation of seizure activity.[87]

Pharmacokinetics

Levetiracetam is well absorbed after oral administration in dogs, with a bioavailability of 100%.[88] Absorption is rapid, with peak concentrations achieved in less than 2 hours.[88,89] The drug is primarily excreted unchanged in the urine of dogs,[90] with an elimination half-life of 3 to 6 hours.[88–91] Although levetiracetam is not metabolized by the liver, concurrent administration of phenobarbital has been shown to increase its clearance, perhaps by inducing its oxidative metabolism in extrahepatic tissues.[92] A pharmacokinetic study in cats demonstrated an oral bioavailability of 100%, with maximum concentrations reached in approximately 1.7 hours and an elimination half-life of approximately 3 hours.[93]

Clinical use

An open-label study evaluating the efficacy of levetiracetam as an add-on treatment in 14 dogs refractory to phenobarbital and bromide documented a response rate of 57%.[94] The efficacy of levetiracetam as add-on therapy was further evaluated in a randomized clinical trial involving 34 dogs with refractory epilepsy.[95] A significant decrease in seizure frequency compared to baseline was observed in levetiracetam-treated dogs; however, no significant change in seizure frequency was identified when levetiracetam treatment was compared with placebo.[95] The use of levetiracetam has also been described in cats, with 7 of 10 cats reported to have a favorable response to treatment.[96]

The recommended dose in both dogs and cats is 20 mg/kg orally every 8 hours. An extended release formulation of the drug is also available, and a pharmacokinetic study supports its use in dogs with a 12-hour dosing interval.[97] Common adverse effects in dogs include sedation and ataxia.[94,95] Lethargy, inappetance, and hypersalivation have been described in cats.[93,96]

A parenteral form of levetiracetam is available for the emergency treatment of seizures. A recent, randomized controlled trial involving 19 dogs demonstrated that IV levetiracetam administered at a dose of 30 mg/kg to 60 mg/kg was safe and potentially effective for the treatment of status epilepticus in dogs.[98]

Pregabalin

Mechanism of action

Pregabalin is a newer-generation drug in the same class as gabapentin. The mechanism of action is similar to gabapentin, although pregabalin has a greater affinity for the binding site by which the drugs exert their effect and consequently has a greater potency than gabapentin.[71]

Pharmacokinetics

A single pharmacokinetic study on oral administration of pregabalin in normal dogs demonstrated that maximum concentrations are achieved at 1.5 hours and an elimination half-life of approximately 7 hours.[99]

Clinical use

There is a single, published, open-label study on the use of pregabalin in dogs with refractory epilepsy, in which 7 of 11 dogs were classified as having a positive response to treatment.[100] The recommended dose for dogs is 3 mg/kg to 4 mg/kg orally every 8 hours; however, in order to minimize side effects, it is suggested that treatment be initiated at 2 mg/kg and the dose increased by 1 mg/kg each week until the target dose

is reached. Common side effects include sedation and ataxia. There are anecdotal reports of the use of pregabalin in cats, with a dose of 1 mg/kg to 2 mg/kg orally every 12 hours most commonly mentioned.

NONPHARMACOLOGIC TREATMENT OPTIONS

Vagal Nerve Stimulation

Alternative, nonmedical methods of seizure control have been explored for patients with epilepsy who experience poor control with antiepileptic medication. One alternative therapy that has proved successful in humans is vagal nerve stimulation. This form of treatment involves the surgical implantation of a pacemaker-type device that delivers repetitive electrical stimulation to the vagus nerve in the neck. A randomized controlled study evaluated vagal nerve stimulation in 10 dogs with refractory epilepsy and found the treatment to be potentially safe and efficacious in some dogs.[101] Due to the expense of the device and the inability to predict whether or not an individual animal will respond, however, this form of therapy is rarely used in veterinary medicine.

Dietary Modification

Dietary modification is another form of nonpharmacologic therapy that has been advocated in the treatment of epilepsy. The ketogenic diet has been used successfully to control seizures in children, and consists of a stringent high-fat, low-carbohydrate, low-protein diet. A randomized controlled study was undertaken to evaluate a ketogenic diet as a treatment for 12 dogs with epilepsy, and no beneficial effect was identified.[102] Other dietary modifications that have been evaluated in dogs include a hypoallergenic diet and fatty acid supplementation. An abstract reporting on a retrospective evaluation of the use of hypoallergenic diet in dogs with poorly controlled seizures described improved seizure control in 7 of 8 dogs, although the full results of this study have not been published in a peer-reviewed source.[103] A randomized controlled trial evaluating the use of essential fatty acid supplementation in 15 dogs with refractory epilepsy found no significant difference in seizure frequency between fatty acid supplementation and placebo.[104] Additional studies are warranted to further explore the potential role of dietary modification in the treatment of epilepsy.

ACUTE MANAGEMENT OF SEIZURES AT HOME

Dogs with poorly controlled seizures place a significant financial and emotional burden on their owners, especially if frequent veterinary visits to obtain emergency care are required. Consequently, the successful management of an epileptic dog should include recommendations for emergency care of seizures at home.

Rectal administration of the parenteral formulation of diazepam has been used most frequently in this regard and has been shown to decrease the number of cluster seizure events over a 24-hour period.[105] The recommended dose is 1 mg/kg of diazepam administered at the onset of seizures, given up to 3 times over a 24-hour period. Dogs receiving phenobarbital should be administered a dose of 2 mg/kg, because chronic phenobarbital therapy reduces peak benzodiazepine concentrations after the administration of rectal diazepam.[60] Diazepam is inactivated by light and adheres to plastic, so the parenteral formulation of the drug should be dispensed in the original glass vial with instructions for the owner to draw up the required amount with a needle and syringe when needed. The needle is then removed, and a rubber catheter or teat cannula is placed on the syringe for rectal administration. Suppository forms of the drug are commercially available, but the pharmacokinetics of these products has not been evaluated in dogs. A recent pharmacokinetic study evaluating a

Table 4
Dose and route of administration for benzodiazepines in the acute management of seizures at home

Drug	Dose	Routes of Administration	References
Diazepam	0.5–1.0 mg/kg	Rectal, intranasal	105,107,108
Midazolam	0.2–0.5 mg/kg	Intranasal, intramuscular[a]	109,110
Lorazepam	0.2 mg/kg	Intranasal[a]	111

[a] Pharmacokinetic studies do not support the administration of either midazolam[110] or lorazepam[112] by the rectal route.

compounded diazepam rectal suppository in dogs demonstated that presumed therapeutic plasma concentrations of diazepam or its active metabolite nordiazepam were not achieved within an acceptable time frame to be effective as emergency treatment for seizures at home.[106]

The parenteral form of diazepam has periodically been unavailable, prompting the need to dispense other benzodiazepines, such as midazolam or lorazepam, for home use. Recommendations of the dose and route of administration are based on pharmacokinetic studies in dogs (**Table 4**), although there are no studies evaluating the efficacy of such treatment in dogs with seizures.

Additional doses of maintenance oral antiepileptic drugs, or pulse therapy with one of the newer drugs, have also been advocated to treat cluster seizures at home, but there are no published reports documenting this use.

REFERENCES

1. Schwartz-Porsche D. Epidemiological, clinical and pharmacokinetic studies in spontaneously epileptic dogs and cats. Proceedings of the 4th Annual American College of Veterinary Internal Medicine Forum, Washington, DC. 1986, 11-61-11-63.
2. Bunch SE. Anticonvulsant drug therapy in companion animals. In: Kirk RW, editor. Current Veterinary Therapy IX. Philadelphia: WB Saunders Co; 1986. p. 836–44.
3. Pakozdy A, Leschnik M, Sarchahi AA, et al. Clinical comparison of primary versus secondary epilepsy in 125 cats. J Feline Med Surg 2010;12:910–6.
4. McNamara JD. Drugs effective in the therapy of epilepsies. In: Hardman JG, Limbird LE, editors. Goodman and Gilman's the pharmacologic basis of therapeutics. New York: McGraw-Hill; 1996. p. 461–85.
5. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676–85.
6. Weissl J, Hülsmeyer V, Brauer C, et al. Disease progression and treatment response of idiopathic epilepsy in Australian shepherd dogs. J Vet Intern Med 2012;26:116–25.
7. Bielfeft SW, Redman HC, McClellan RO. Sire- and sex-related differences in rates of epileptiform seizures in a purebred Beagle dog colony. Am J Vet Res 1971;32:2039–48.
8. Famula TR, Oberhauer AM. Segregation analysis of epilepsy in the Belgian Tervueren dog. Vet Rec 2000;147:218–21.
9. Kathmann I, Jaggy A, Busato A, et al. Clinical and genetic investigations of idiopathic epilepsy in the Bernese Mountain dog. J Small Anim Pract 1999;40:319–25.

10. Hülsmeyer V, Zimmermann R, Brauer C, et al. Epilepsy in Border collies: clinical manifestation, outcome and mode of inheritance. J Vet Intern Med 2010;24: 171–8.
11. Lohi H, Young EJ, Fitzmaurice SN, et al. Expanded repeat in canine epilepsy. Science 2005;307:81.
12. Licht BG, Licht MH, Harper KM, et al. Clinical presentation of naturally occurring canine seizures: similarities to human seizures. Epilepsy Behav 2002;3:460–70.
13. Patterson EE, Armstrong JP, O'Brien DR, et al. Clinical description and mode of inheritance of idiopathic epilepsy in English Springer Spaniels. J Am Vet Med Assoc 2005;226:54–8.
14. Falco MJ, Barker J, Wallace ME. The genetics of epilepsy in the British Alsatian. J Small Anim Pract 1974;15:685–92.
15. Srenk P, Jaggy A. Interictal electroencephalographic findings in a family of Golden Retrievers with idiopathic epilepsy. J Small Anim Pract 1996;37:317–21.
16. Casal ML, Munuve RM, Janis MA, et al. Epilepsy in Irish Wolfhounds. J Vet Intern Med 2006;20:131–5.
17. Hall SJ, Wallace ME. Canine epilepsy: a genetic counseling programme for Keeshounds. Vet Rec 1996;138:358–60.
18. Jaggy A, Faissler D, Gaillard C, et al. Genetic aspects of idiopathic epilepsy in Labrador Retrievers. J Small Anim Pract 1998;39:275–80.
19. Jokinen TS, Metsähonkala L, Bergamasco L, et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. J Vet Intern Med 2007;21:464–71.
20. Morita T, Shimada A, Takeuchi T, et al. Cliniconeuropathologic findings of familial frontal lobe epilepsy in Shetland Sheepdogs. Can J Vet Res 2002;66:35–41.
21. Licht BG, Lin S, Luo Y, et al. Clinical characteristics and mode of inheritance of familial focal seizures in Standard Poodles. J Am Vet Med Assoc 2007;231: 1520–8.
22. Patterson EE, Mickelson JD, Da Y, et al. Clinical characteristics and inheritance of idiopathic epilepsy in Vizslas. J Vet Intern Med 2003;17:319–25.
23. Heynold Y, Faissler D, Steffen F, et al. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 Labrador retrievers: a long-term study. J Small Anim Pract 1997;38:7–14.
24. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.
25. Jull P, DeRisio L, Horton C, et al. Effect of prolonged status epilepticus as a result of intoxication on epileptogenesis in a UK canine population. Vet Rec 2011;169:361–4.
26. Shovron S, Luciano AL. Prognosis of chronic and newly diagnosed epilepsy: revisiting temporal aspects. Curr Opin Neurol 2007;20:208–12.
27. Rogawski MA, Johsnon MR. Intrinsic severity as a determinant of antiepileptic drug refractoriness. Epilepsy Curr 2008;8:127–30.
28. Muñana KR, Nettifee-Osborne JA, Bergman RL, et al. Association between ABCB 1 genotype and seizure outcome in Collies with epilepsy. J Vet Intern Med 2012;26:1358–64.
29. Leppik IE. Monotherapy and polytherapy. Neurology 2000;55:S25–9.
30. Muñana KR, Zhang D, Patterson EE. Placebo effect in canine epilepsy trials. J Vet Intern Med 2010;24:166–70.
31. Podell M. Seizures in dogs. Vet Clin North Am Small Anim Pract 1996;26: 779–810.
32. Berendt M, Gredal H, Kjaer Ersboll A, et al. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med 2007;21:754–9.

33. Twyman RE, Rogers CJ, Macdonald RL. Differential regulation of gamma-aminobutyric acid receptor channels by diazepam and phenobarbital. Ann Neurol 1989;25:213–20.
34. Heyer E, Macdonald R. Barbiturate reduction of calcium-dependent action potentials: correlation with anesthetic action. Brain Res 1982;236:157–71.
35. Pedersoli WM, Wike JS, Ravis WR. Pharmacokinetics of single doses of phenobarbital given intravenously and orally to dogs. Am J Vet Res 1987;48:679–83.
36. Al-Tahan F, Frey HH. Absorption kinetics and bioavailability of phenobarbital after oral administration to dogs. J Vet Pharmacol Ther 1985;8:205–7.
37. Ravis WR, Nachreiner RF, Pedersoli WM, et al. Pharmacokinetics of phenobarbital in dogs after multiple oral administration. Am J Vet Res 1984;45:1283–6.
38. Ravis WR, Pedersoli WM, Wike JS. Pharmacokinetics of phenobarbital in dogs given multiple doses. Am J Vet Res 1989;50:1343–7.
39. Cochrane SM, Black WD, Parent JM, et al. Pharmacokinetics of phenobarbital in the cat following intravenous and oral administration. Can J Vet Res 1990;54:132–8.
40. Cochrane SM, Parent JM, Black WD, et al. Pharmacokinetics of phenobarbital in the cat following multiple oral administration. Can J Vet Res 1990;54:309–12.
41. Wilensky A, Friel P, Levy R, et al. Pharmacokinetics of phenobarbital in normal subjects and epileptic patients. Eur J Clin Pharmacol 1982;23:87–92.
42. Schwartz-Porsche D, Loscher W, Frey HH. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. J Vet Pharmacol Ther 1985;8:113–9.
43. Farnbach GC. Serum concentrations and efficacy of phenytoin, phenobarbital, and primidone in canine epilepsy. J Am Vet Med Assoc 1984;184:1117–20.
44. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. J Am Vet Med Assoc 2012;240:1073–83.
45. Schwartz-Porsche D, Kaiser E. Feline epilepsy. Probl Vet Med 1989;1:629–49.
46. Levitski RE, Trepanier LA. Effect of timing of blood collection on serum phenobarbital concentrations in dogs with epilepsy. J Am Vet Med Assoc 2000;217:200–4.
47. Boothe DM. Anticonvulsant therapy in small animals. Vet Clin North Am Small Anim Pract 1998;28:411–48.
48. Quesnel AE, Parent JM, McDonell W. Clinical management and outcome of cats with seizure disorders: 30 cases (1991-1993). J Am Vet Med Assoc 1997;210:72–7.
49. Kube SA, Vernau KM, LeCouteur RA. Dyskinesia associated with oral phenobarbital administration in a dog. J Vet Intern Med 2006;20:1238–40.
50. Jacobs G, Calvert C, Kaufman A. Neutropenia and thrombocytopenia in three dogs treated with anticonvulsants. J Am Vet Med Assoc 1998;212:681–4.
51. Chauvet AE, Feldman EC, Kass PH. Effects of phenobarbital administration on results of serum biochemical analyses and adrenocortical function tests in epileptic dogs. J Am Vet Med Assoc 1995;207:1305–7.
52. Foster SF, Church DB, Watson ADJ. Effects of phenobarbitone on serum biochemical tests in dogs. Aust Vet J 2001;78:23–6.
53. Müller PB, Taboada J, Hosgood G, et al. Effects of long-term phenobarbital treatment on the liver in dogs. J Vet Intern Med 2000;14:165–71.
54. Gaskill CL, Miller LM, Mattoon JS, et al. Liver histopathology and liver and serum alanine aminotransferase and alkaline phosphatase activities in epileptic dogs receiving phenobarbital. Vet Pathol 2005;42:147–60.

55. Dayrell-Hart B, Steinberg SA, VanWinkle TJ, et al. Hepatotoxicity of phenobarbital in dogs: 18 cases (1985-1989). J Am Vet Med Assoc 1991;199:1060–6.
56. Kantrowitz LB, Peterson ME, Trepanier LA, et al. Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in epileptic dogs treated with anticonvulsants. J Am Vet Med Assoc 1999;214:1804–8.
57. Gaskill CL, Burton SA, Gelens HC, et al. Effects of phenobarbital treatment on serum thyroxine and thyroid-stimulating hormone concentrations in epileptic dogs. J Am Vet Med Assoc 1999;215:489–96.
58. Müller PB, Wolfsheimer KJ, Taboada J, et al. Effects of long-term phenobarbital treatment on the thyroid and adrenal axis and adrenal function tests in dogs. J Vet Intern Med 2000;14:157–63.
59. Orito K, Saito M, Fukunaga K, et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. J Vet Pharmacol Ther 2008;31:259–64.
60. Wagner SO, Sams RA, Podell M. Chronic phenobarbital therapy reduces plasma benzodiazepine concentrations after intravenous and rectal administration of diazepam in the dog. J Vet Pharmacol Ther 1998;21:335–41.
61. Lord LK, Podell M. Owner perception of the care of long-term phenobarbital-treated epileptic dogs. J Small Anim Pract 1999;40:11–5.
62. Uthman BM. Less commonly used antiepileptic drugs. In: Wyllie E, Casciano GD, Gidal BE, et al, editors. Wyllie's treatment of epilepsy Principles and practice. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 779–89.
63. Trepanier LA, Babish JG. Pharmacokinetic properties of bromide in dogs after the intravenous and oral administration of single doses. Res Vet Sci 1995;58:248–51.
64. Boothe DM, George KL, Couch P. Disposition and clinical use of bromide in cats. J Vet Med Assoc 2002;221:1131–5.
65. Trepanier LA, Babish JG. Effect of dietary chloride content on bromide elimination and dosage in dogs. Res Vet Sci 1995;58:252–5.
66. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. J Vet Intern Med 1993;7:318–27.
67. Trepanier LA, Van Schoick A, Schwark WS, et al. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992-1996). J Am Vet Med Assoc 1998;213:1449–53.
68. Gaskill CL, Cribb AE. Pancreatitis associated with potassium bromide/phenobarbital combination therapy in epileptic dogs. Can Vet J 2000;41:555–8.
69. Rossmeisl JH, Inzana KD. Clinical signs, risk factors, and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy. J Am Vet Med Assoc 2009;234:1425–31.
70. Nichols EF, Trepanier LA, Linn K. Bromide toxicosis secondary to renal insufficiency in an epileptic dog. J Am Vet Med Assoc 1996;208:231–3.
71. Sills GJ. The mechanism of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006;6:108–13.
72. Radulovic LL, Türck D, Von Hodenberg A, et al. Disposition of gabapentin (Neurontin) in mice, rats, dogs and monkeys. Drug Metab Dispos 1995;23:441–8.
73. Vollmer KO, von Hodenberg A, Kölle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimittelforschung 1986;36:830–9.
74. Platt SR, Adams V, Garosi LS, et al. Treatment with gabapentin of 11 dogs with refractory idiopathic epilepsy. Vet Rec 2006;159:881–4.

75. Govendir M, Perkins M, Malik R. Improving seizure control in dogs with refractory epilepsy using gabapentin as an adjunctive agent. Aust Vet J 2005;83:602–8.
76. Dunayer EK, Gwaltnew-Brant SM. Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs. J Am Vet Med Assoc 2006;229:1113–7.
77. Holder JL Jr, Wilfond AA. Zonisamide in the treatment of epilepsy. Expert Opin Pharmacother 2011;12:2573–81.
78. Boothe DM, Perkins J. Disposition and safety of zonisamide after intravenous and oral single dose and oral multiple dosing in normal hound dogs. J Vet Pharmacol Ther 2008;31:544–53.
79. Hasegawa D, Kobayashi M, Kuwabara T, et al. Pharmacokinetics and toxicity of zonisamide in cats. J Feline Med Surg 2008;10:418–21.
80. Dewey CW, Guiliano R, Boothe DW, et al. Zonisamide therapy for refractory idiopathic epilepsy in dogs. J Am Anim Hosp Assoc 2004;40:285–91.
81. von Klopmann T, Rambeck B, Tipold A. Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. J Small Anim Pract 2007;48:134–8.
82. Chung JY, Hwang CY, Chae JS, et al. Zonisamide monotherpy for idiopathic epilepsy in dogs. N Z Vet J 2012;60:357–9.
83. Miller ML, Center SA, Randolph JF, et al. Apparent acute idiosyncratic hepatic necrosis associated with zonisamide administration in a dog. J Vet Intern Med 2011;25:1156–60.
84. Schwartz M, Muñana KR, Olby NJ. Possible drug-induced hepatopathy in a dog receiving zonisamide monotherapy for treatment of cryptogenic epilepsy. J Vet Med Sci 2011;73:1505–8.
85. Cook AK, Allen AK, Espinosa D, et al. Renal tubular acidosis associated with zonisamide therapy in a dog. J Vet Intern med 2011;25:1454–7.
86. Lynch BA, Lamberg N, Nocka K, et al. The synaptic vesicle protein SVA2 is the binding site for the antiepileptic drug LEV. Proc Natl Acad Sci 2004;101:9861–6.
87. Surges R, Volynski KE, Walker MC. Is levetiracetam different from other antiepileptic drugs? Levetiracetam and its cellular mechanism of action in epilepsy revisited. Ther Adv Neurol Disord 2008;1:13–24.
88. Patterson EE, Goel V, Cloyd JC, et al. Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics. J Vet Pharmacol Ther 2008;31:253–8.
89. Moore SA, Muñana KR, Papich MG, et al. Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. Am J Vet Res 2010;71:337–41.
90. Isoherranen N, Yagen B, Soback S, et al. Pharmacokinetics of levetiracetam and its enantiomer (R)-alpha-ethyl-2-oxo-pyrrolidine acetamide in dogs. Epilepsia 2001;42:825–30.
91. Dewey CW, Bailey KS, Boothe DM, et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. J Vet Emerg Crit Care 2008;18:153–7.
92. Moore SA, Muñana KR, Papich MG, et al. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. J Vet Pharmacol Ther 2010;34:31–4.
93. Carnes MB, Axlund TW, Boothe DM. Pharmacokinetics of levetiracetam after oral and intravenous administration of a single dose to clinically normal cats. Am J Vet Res 2011;72:1247–52.

94. Volk HA, Matiasek LA, Luján Feliu-Pascual A, et al. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. Vet J 2008;176:310–9.
95. Muñana KR, Thomas WB, Inzana KD, et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled crossover trial. J Vet Intern Med 2012;26:341–8.
96. Bailey KS, Dewey CW, Boothe DM, et al. Levetiracetam as an adjunct to phenobarbital treatment in cats with suspected idiopathic epilepsy. J Am Vet Med Assoc 2008;232:867–72.
97. Beasley MJ, Boothe DM. The pharmacokinetics of single dose extended release Keppra® with and without food in healthy adult dogs [abstract]. J Vet Intern Med 2012;26:819.
98. Hardy BT, Patterson EE, Cloyd JM, et al. Double-masked, placebo-controlled study of intravenous levetiracetam for the treatment of status epilepticus and acute repetitive seizures in dogs. J Vet Intern Med 2012;26:334–40.
99. Salazar V, Dewey CW, Schwark W, et al. Pharmacokinetics of single-dose oral pregabalin administration in normal dogs. Vet Anaesth Analg 2009;36:574–80.
100. Dewey CW, Cerda-Gonzalz S, Levine JM, et al. Pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy. J Am Vet Med Assoc 2009;235:1442–9.
101. Muñana KR, Vitek SM, Tarver WB, et al. Use of vagal nerve stimulation as a treatment for refractory epilepsy in dogs. J Am Vet Med Assoc 2002;221:977–83.
102. Patterson EE, Muñana KR, Kirk CA, et al. Results of a ketogenic food trial for dogs with idiopathic epilepsy [abstract]. J Vet Intern Med 2005;19:421.
103. Luján A, Scott SD, Anderson TJ. The role of diet in refractory canine epilepsy – a retrospective case series [abstract]. In: BSAVA Congress 2004: Scientific Proceedings. Quedgeley, UK: British Small Animal Veterinary Association; 2004. p. 53.
104. Matthews H, Granger N, Wood J, et al. Effects of essential fatty acid supplementation in dogs with idiopathic epilepsy: a clinical trial. Vet J 2012;191:396–8.
105. Podell M. The use of diazepam per rectum at home for the acute management of cluster seizures in dogs. J Vet Intern Med 1995;8:68–74.
106. Probst CW, Thomas WB, Moyers TD, et al. Evaluation of plasma diazepam and nordiazepam concentrations following administration of diazepam intravenously or via suppository per rectum in dogs. Am J Vet Res 2013;74:611–5.
107. Platt SR, Scott KC, Chrisman CL, et al. Comparison of plasma benzodiazepine concentrations following intranasal and intravenous administration of diazepam to dogs. Am J Vet Res 2000;61:651–4.
108. Musulin SE, Mariani CL, Papich MG. Diazepam pharmacokinetics after nasal drop and atomized nasal administration in dogs. J Vet Pharmacol Ther 2011; 34:17–24.
109. Eagleson JS, Platt SR, Elder Strong DL, et al. Bioavailability of a novel midazolam gel after intranasal administration in dogs. Am J Vet Res 2012;73:539–45.
110. Schwartz M, Muñana KR, Nettifee-Osborne JA, et al. The pharmacokinetics of midazolam after intravenous, intramuscular, and rectal administration in healthy dogs. J Vet Pharmacol Ther 2012 Dec 19 [Epub ahead of print].
111. Mariani CL, Clemmons RM, Lee-Ambrose L, et al. A comparison of intranasal and intravenous lorazepam in normal dogs [abstract]. J Vet Intern Med 2003;17:402.
112. Podell M, Wagner SO, Sams RA. Lorazepam concentrations in plasma following its intravenous and rectal administration in dogs. J Vet Pharmacol Ther 1998;21: 158–60.