Seizures in Young Dogs and Cats: Management*

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ABSTRACT:
Seizures in immature animals may require treatment. When the underlying cause of seizures cannot be determined or corrected or recurrent seizures are expected, antiepileptic drug therapy is generally recommended. Before administering antiepileptic drug therapy in immature animals, there are special considerations for the liver and kidneys. Specific details for phenobarbital, potassium bromide, and alternative antiepileptic drugs are discussed in this article. Other specific therapies are indicated for structural and metabolic disorders.

S eizure management in immature (i.e., younger than 6 months of age) dogs or cats can be a challenging clinical problem. Clinicians presented with puppies or kittens (i.e., 3 to 12 weeks of age) having seizures are faced with unique considerations. The underlying cause of a seizure disorder may be distinct in mature animals but sometimes vague in immature animals. Developmental concerns must also be considered before administering drugs to immature animals. Immature patients require special consideration regarding growth and development of various organ systems responsible for drug metabolism and elimination. Limited information is available regarding optimal treatment of seizures in neonatal (younger than 2 weeks of age) and immature dogs and cats. Every attempt should be made to identify the underlying cause of seizures.

DECIDING TO TREAT
Considering the potential effects of antiepileptics on brain development and the effort and expense of administering the drugs, the decision to treat an immature animal with seizures should be based on objective criteria as suggested by previous reports. Long-term antiepileptic therapy is recommended when an identifiable structural abnormality of the brain, such as hydrocephalus, exists. A history of head trauma in a patient that has seizures may warrant treatment; seizures may begin soon after the trauma or months later. An episode of status epilepticus warrants ongoing antiepileptic therapy unless the cause, such as toxin exposure, is identified and remedied. The occurrence of two seizures within 8 weeks or two cluster seizures within 12 weeks may also justify antiepileptic therapy. The term cluster seizures is used when two or more seizures occur within 24 hours.

Selecting an antiepileptic and designing a dosing regimen are more complicated in
young patients than mature ones. Specific therapeutic aims should be discussed with the owner. The ideal treatment goal is to completely stop seizures without causing drug-related side effects. However, a more realistic goal of antiepileptic therapy in pediatric patients is acceptable seizure control with minimal drug-related side effects or toxicity. It is important to make pet owners aware that even when therapy has been initiated, adequate control may be difficult because seizure activity can worsen. “Acceptable control” varies from client to client, but approximately one seizure every 4 to 6 weeks is generally an acceptable target.

**SPECIFIC CONSIDERATIONS FOR YOUNG ANIMALS**

Unfortunately, limited clinical information exists regarding administration of antiepileptics in dogs and cats younger than 6 months of age. Information is often extrapolated from study results in mature animals and humans. Pharmacokinetic data and drug disposition information are interpreted with caution when extrapolating between species and ages.

**DRUG DISPOSITION**

Anticonvulsant drug disposition in young animals may be different than that in adult (i.e., 3 to 6 months old). In young animals, anticonvulsant drug disposition may be different than in adult animals due to slower gastric emptying, slower drug absorption, and lower drug concentrations. Higher intestinal permeability may lead to more drug entering the systemic circulation and causing toxicosis. Increased amount of body water, with a shift in the amount in the extracellular space, can affect drug distribution and metabolism.

### Table 1. Differences in Drug Disposition in Puppies and Kittens as well as Considerations for Anticonvulsant Administration

<table>
<thead>
<tr>
<th>Aspect of Drug Disposition</th>
<th>Potential Effect</th>
<th>Recommended Antiepileptic Drug</th>
<th>Relative Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slower gastric emptying/motility</td>
<td>Slower drug absorption and lower drug concentrations</td>
<td>All</td>
<td>Minor</td>
</tr>
<tr>
<td>Higher intestinal permeability</td>
<td>More drug enters the systemic circulation and causes toxicosis</td>
<td>All oral antiepileptics</td>
<td>Minor</td>
</tr>
<tr>
<td>Increased amount of body water, with a shift in the amount in the extracellular space</td>
<td>Increased drug distribution, which lowers eventual peak drug concentrations</td>
<td>Bromide</td>
<td>Major: may need to increase the amount given each time and lengthen the dose interval</td>
</tr>
<tr>
<td>Lower serum protein concentration</td>
<td>Drugs with high protein binding have more active drug available for actual drug effects; this could increase the half-life of the drug and result in toxicity if standard dosing regimens are used</td>
<td>Most antiepileptics are not highly protein bound</td>
<td>Minor</td>
</tr>
<tr>
<td>Less body fat</td>
<td>Lipid-soluble drugs have less accumulation, Higher peak concentration of the drug</td>
<td>None</td>
<td>Minor</td>
</tr>
<tr>
<td>Decreased phase 1 hepatic metabolism</td>
<td>Clearance is reduced: The half-life may be longer, resulting in a higher concentration of the drug and potential toxicity</td>
<td>Phenobarbital (may need to lower the drug dose and increase the interval)</td>
<td>Major</td>
</tr>
<tr>
<td>Decreased phase 2 hepatic metabolism</td>
<td>Pro-drugs are not activated, Treatment is not effective</td>
<td>Primidone</td>
<td>Minor</td>
</tr>
<tr>
<td>Renal function</td>
<td>Reduced clearance leads to an increased half-life and potential toxicity</td>
<td>Bromide</td>
<td>Minor</td>
</tr>
</tbody>
</table>
of age) animals (Table 1). Consideration of these differences is important to avoid plasma drug concentrations that may lead to toxicosis or subtherapeutic concentrations and treatment failure. The four determinants of drug disposition include absorption, distribution, metabolism, and clearance.

**Absorption**

The first component of drug disposition is absorption, which depends on oral or parenteral drug administration. Orally administered drugs have a slower gastric emptying time (Table 2). Reduced gastrointestinal motility could result in slower drug absorption, causing lower systemic drug levels and reduced drug efficacy. Oral dosing in young animals does not usually present much of a problem with well-absorbed drugs such as phenobarbital and bromide.

Parenteral drug administration is often necessary in emergencies. In neonatal animals, venous access may be difficult to obtain. Therefore, an intraosseous catheter may be effective in administering anticonvulsants and fluids. It has been shown in dogs that intraosseous infusion of diazepam or phenobarbital results in serum levels comparable with intravenous administration of the same drugs. Intraosseous infusion allows rapid delivery of anticonvulsants in emergencies. It is important to properly place an intraosseous catheter because repeated attempts with subsequent bone trauma allow extravasation of phenobarbital or, conceivably, diazepam.

Additional alternate routes for parenteral drug delivery may be needed for initial drug administration until an intravenous or intraosseous catheter can be placed. In an emergency, phenobarbital may also be injected intraperitoneally. Rectal administration of diazepam and other drugs allows an alternate route compared with intravenous drug administration and offers rapid drug absorption, at least in dogs. Diazepam may also be absorbed via nasal administration.

### Table 2. Suggested Oral Drug Doses in Puppies and Kittens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Species and Dose</th>
<th>Age-Specific Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td><em>Cats and dogs</em>: 2 mg/kg bid</td>
<td>Immature liver function</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td><em>Dogs</em>: 30–40 mg/kg/day, <em>Cats</em>: 10–20 mg/kg/day</td>
<td>Renal elimination, no protein binding, volume of distribution, large impact</td>
</tr>
<tr>
<td>Diazepam</td>
<td><em>Cats</em>: 0.25–0.5 mg/kg tid</td>
<td>—</td>
</tr>
<tr>
<td>Clorazepate</td>
<td><em>Dogs</em>: 0.5–1 mg/kg tid or 2 mg/kg q12h</td>
<td>—</td>
</tr>
<tr>
<td>Gabapentin</td>
<td><em>Cats and dogs</em>: 10 mg/kg tid</td>
<td>Renal elimination, minimal protein binding, and a larger volume of distribution may make clearance more rapid</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td><em>Cats and dogs</em>: 20 mg/kg tid, increase the dose in 20 mg/kg increments</td>
<td>Renal elimination, minimal protein binding</td>
</tr>
<tr>
<td>Zonisamide</td>
<td><em>Dogs</em>: 10 mg/kg bid with phenobarbital or 5 mg/kg bid without phenobarbital</td>
<td>Renal elimination, taken up by erythrocytes</td>
</tr>
<tr>
<td>Felbamate</td>
<td>15 mg/kg tid</td>
<td>A shorter dose interval may be needed because of rapid metabolism in puppies</td>
</tr>
</tbody>
</table>

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**Distribution**

Drug distribution depends on transport to storage sites and target organs. This process is altered by drug binding to protein, which prevents drug distribution to the target organ. Protein binding impacts drug availability, also called *free drug*, which acts on the target organ. Differences in drug distribution in young animals are expected because of a lower plasma albumin concentration. The volume of distribution is characterized by a greater percentage of total body water, a proportionately greater extracellular compartment, and a smaller percentage of body fat. An important factor regarding distribution is the difference in volume of distribution in neonates and young animals compared with that in adults. In neonates and young animals, there is an increased amount of body water with a shift in the amount of water in the extracellular space. Neonates have 80% to 85% total body water, whereas adults have 55% to 60%. The extracellular fluid component in neonates may be double that in adults. At birth, the total body water in dogs is 84%; it drops to 68% by 3 months of age and 63% by 6 months of age. At these ages, the proportions of extracellular fluid are 53%, 37%, and 32%, respectively. The increase in total body water and proportion of extracellular fluid results in a larger volume of distribution, which can impact the distribution of water-soluble drugs such as bromide.

Increased drug distribution lowers the eventual peak drug concentration. A larger volume of distribution may increase the required dose of a specific drug:

\[
\text{Drug dose} = \frac{\text{Volume of distribution}}{\text{Plasma concentration}}
\]

Drug elimination and the subsequent half-life may be longer and require a longer dosing interval. This can be overcome by increasing the drug dose and lengthening the dose interval.

Neonates and young animals have a lower serum protein concentration because they have less albumin than do adults. Albumin and total protein concentration approach adult levels by 8 weeks of age. This difference in young animals has an impact on drugs with high protein binding. A highly bound drug is considered to be greater than 80% protein bound. A lower protein concentration allows more active drug to exert pharmacologic effects on target organs. Standard dosing of a drug when less protein binding occurs could increase the half-life of the drug and result in toxicity if standard dosing regimens are used. Reduced protein binding is probably not significant for standard anticonvulsants because most are not considered to be highly protein bound. However, dose reduction or prolonged intervals between drug administration may be indicated for drugs that are highly protein bound.

A lower amount of body fat is of less concern regarding antiepileptic drug distribution in young animals. The peak concentration is higher because of less accumulation of lipid-soluble drugs. A lower dose is administered with drugs that have high lipid solubility.

Circulatory factors may have a minor influence in distribution of antiepileptics in young animals. Reduced renal blood flow may decrease elimination. Increased blood volume to the brain and a more permeable blood–brain barrier in very young patients may lead to more signs of toxicity (e.g., sedation).

**Metabolism**

Specific hepatic metabolic mechanisms mature at different rates. In young animals, there is a reduction in phase 1 (i.e., oxidation) and 2 (i.e., drug activation) hepatic metabolism. This is important for antiepileptics such as phenobarbital and primidone, in which phenobarbital is the main active metabolite. Lack of hepatic enzyme metabolism can result in improper drug activation. At 4 to 6 weeks of age, hepatic clearance of drugs is near adult capabilities. By 5 to 8 weeks of age, hepatic enzyme activities in puppies are equivalent to those in mature dogs. By about day 135, cytochrome P-450 and various other hepatic enzymes are found at levels comparable with those in adults. With reduced hepatic metabolism, there may be an increased plasma half-life, decreased plasma clearance, and toxicosis. The dose may need to be lowered and the interval of administration increased.

**Clearance**

Drug clearance is mainly determined by renal function. Renal clearance is lower in neonates but close to adult levels by 4 weeks of age. Reduced renal function is due to a reduced glomerular filtration rate (GFR) and renal blood flow as well as immature tubular secretion. The GFR increases by 2 weeks of age. Adult renal tubular function and GFR are attained by 8 weeks of age. Renal tubular solute resorption differs, depending on the solute, which matures at different rates.
Regarding antiepileptics, this is particularly important for potassium bromide. Reduced renal clearance results in an increased drug half-life and potential toxicosis. This is important for water-soluble anticonvulsants such as bromide and gabapentin. Less drug is administered over longer dosing intervals. Diazepam may also have a prolonged half-life in animals with reduced renal function.

Pediatric Animals
Because of age differences in drug disposition, adult dosing regimens for antiepileptics can be administered by 3 months of age. However, doses need to be adjusted with continued growth to maintain therapeutic serum levels. Also, as an animal matures, the volume of distribution changes with a shift in the amount of extracellular body water.

FIRST-LINE ANTICONVULSANT THERAPY
Phenobarbital
The barbiturate phenobarbital has proven efficacy as an antiepileptic in dogs and cats. Monotherapy of phenobarbital is effective in 60% to 90% of adult dogs. Boothe et al showed that phenobarbital ameliorated seizure activity in 85% of adult dogs and reduced seizure activity by at least 50% in 90% of adult dogs.

Phenobarbital is well absorbed, with 90% available orally in dogs. It does not have significant protein binding, with only 40% to 50% being protein bound. In humans, 50% of phenobarbital is protein bound; however, less is bound in neonates. The elimination half-life of phenobarbital is 37 to 74 hours in dogs and 34 to 43 hours in cats. The half-life of phenobarbital decreases with long-term administration because the drug is a hepatic enzyme autoinducer. Phenobarbital elimination mainly consists of metabolism by hepatic microsomal enzymes; however, 25% of the drug is excreted unchanged by the kidneys as a result of a pH-dependent process.

It has been shown in neonatal puppies that various enzymes involved in phenobarbital metabolism increase significantly within the first 4 to 6 weeks of life. Also, repeated administration of phenobarbital induces P-450 and bilirubin glucuronyl transferase. Distribution of phenobarbital at a dose of 15 mg/kg IV, IO, or PO has been evaluated in puppies as young as 4 days of age. Phenobarbital is slowly eliminated from plasma at similar rates in 4- and 60-day-old puppies.

The optimal dose in young animals is unknown, but because canine hepatic enzyme activities may reach adult levels by 5 weeks of age, a normal adult dose can be administered. Serum phenobarbital levels should be monitored to support the recommended starting dose of 2 to 3 mg/kg IV, IO, or PO q12h. The phenobarbital dose may need to be lower in animals younger than 4 weeks of age, and the interval between doses may need to be increased. Diet, body weight, and body composition may also alter the required dose. Phenobarbital clearance in dogs may change with alterations in body composition.

Drug-induced hepatotoxicity in dogs has been well described in the literature and is more likely to occur in animals with serum concentrations above 35 µg/ml. Because phenobarbital is a hepatic enzyme inducer, drug efficacy can be altered. Phenobarbital can also alter the response to other drugs, including anesthetics, in immature animals.

Phenobarbital may have an effect on central nervous system development, specifically mental impairment. Neonatal rats receiving phenobarbital had disturbances in brain growth regarding overall brain weights and the amounts of DNA, RNA, cholesterol, and protein compared with normal brains, but no effect on body weight was noted. One possible problem with phenobarbital administration during development is the impact on the intelligence quotient. However, other evaluations of children receiving long-term phenobarbital for seizures have not found effects on mental development.

Bromide
Bromide, the oldest known effective anticonvulsant administered in humans, has gained popularity as an antiepileptic in dogs in recent years. Although its
Seizures in immature animals may require treatment, especially if recurrent seizures occur more often than every 4 to 6 weeks and with status epilepticus or cluster seizures.

use has been advocated in cats, reports of respiratory side effects and a lack of proved efficacy make this a less desirable anticonvulsant in cats. Bromide is effective as monotherapy in adult dogs. It was shown to eradicate seizures in 65% of dogs in a study by Boothe et al. This was less effective than phenobarbital; however, it did reduce seizure frequency (in 83% of dogs) similar to phenobarbital administration. Bromide administration has been shown to reduce seizure frequency by at least 50% in 72% of dogs, including those refractory to phenobarbital. When bromide is administered with phenobarbital, 34% of dogs can have their dose of phenobarbital reduced and phenobarbital can be discontinued in 19%. Reports of bromide administration in puppies and kittens are lacking. Although bromide is not commonly administered in humans, one of its main uses has been in infants and children with refractory epilepsy, with no apparent long-term side effects of the drug.

Bromide is generally administered as potassium salt. It is water soluble, well absorbed orally, and absorbed 60% rectally. It is distributed in extracellular fluid in a manner similar to that of chloride (0.2 to 0.4 L/kg). This drug is not protein bound. The half-life is 25 days in dogs and 10 days in cats. Bromide is eliminated by the kidneys in a manner similar to that of chloride (i.e., tubular elimination) and does not undergo hepatic metabolism.

The important pharmacokinetic consideration for bromide administration in young animals is the difference between volume of distribution and renal elimination. A change in total body water and extracellular water may affect bromide distribution in younger animals. Puppies have a larger percentage of body water, resulting in a greater volume of distribution. This leads to reduced clearance of bromide and a longer serum half-life. Adult renal function is obtained by 2½ months of age. Because renal elimination is slower in animals younger than 4 weeks, the bromide dose and frequency should be altered. Bromide toxicity has been reported secondary to renal insufficiency. Therefore, it has been suggested that the initial dose of bromide be reduced to half when renal function is impaired.

The half-life of bromide is approximately 25 days in dogs and is somewhat diet dependent. Steady state is attained in 3 to 6 months, but clinical response is attained much sooner. The initial dose should be 30 to 40 mg/kg PO as an adjunct to phenobarbital and 40 mg/kg PO when administered alone. The higher end of the dose range is dictated by side effects of the drug and not by serum levels. The dose can be increased gradually until seizures are controlled or side effects are unacceptable. Individual animals respond differently to varying serum levels. This drug has been associated with a narrow therapeutic index. Typical side effects of bromide include polydipsia, polyuria, and polyphagia. It has also been associated with pancreatitis in dogs.

**First Choice**

Although dosing regimens differ, pediatric and adult seizures can be treated with the same anticonvulsant. Because of changes that occur in developing animals until 3 months of age, phenobarbital or bromide is an acceptable choice of anticonvulsant. In animals younger than 3 months of age, phenobarbital may be easier to administer because of its pharmacokinetic properties, shorter half-life, and more rapid seizure control. Phenobarbital is probably a better first-choice anticonvulsant (except in patients with overt liver dysfunction and recurrent seizures) because of its shorter half-life and the ease of adjusting the dose as patients gain weight or the seizures become difficult to manage. In cases of liver disease (i.e., a hepatic portosystemic shunt is causing seizures), bromide may be a better choice.

**Benzodiazepines**

Benzodiazepines are considered safe to administer in young animals. Hepatic metabolism of these drugs may be slower than that of other drugs. Diazepam and
its major metabolite desmethyl diazepam rapidly cross the blood–brain barrier and reach steady-state concentrations that correlate to the unbound portion of the drug in dogs. In dogs, diazepam is 96% protein bound and desmethyl diazepam is 95.9% protein bound. Clearance of these drugs from cerebrospinal fluid (CSF) is determined by plasma protein binding. The unbound portion of the drug is therefore the component that exerts its effects on the nervous system. The lower protein binding in neonates may result in more profound side effects.

According to electroencephalography, diazepam stops seizures in neonatal dogs experiencing experimentally induced seizures. Although brain energy levels quickly normalized after diazepam administration, increased tissue lactate concentrations require longer periods to normalize.

Benzodiazepines are not recommended for long-term administration in dogs because seizures eventually become refractory. Tolerance is a process by which an anticonvulsant no longer controls seizures in a patient receiving the drug over a period of time. Functional tolerance (versus metabolic tolerance [i.e., more rapid drug elimination]) was shown to develop in dogs, possibly within 1 week of treatment. This is less likely to occur in cats. In cats, diazepam may be administered as a primary or secondary antiepileptic at a dose of 0.25 to 0.5 mg/kg PO tid. However, reports of idiosyncratic hepatotoxicity with oral administration make this drug less appealing. This more commonly occurs within 11 days of starting treatment with the drug.

Clorazepate is another benzodiazepine that may be administered to control seizures in dogs and cats. Clorazepate tolerance does not develop as quickly as diazepam tolerance in dogs. Clorazepate is hydrolyzed to nordiazepam in the stomach and metabolized by the liver. The half-life is reportedly 3 to 6 hours in dogs. A recommended dose is 0.5 to 1 mg/kg PO tid. Another suggested dose is 2 mg/kg PO q12h. Clorazepate is available in a sustained-release formulation, but regular-release tablets are adequate for dogs. Nordiazepam is measured for therapeutic monitoring (suggested therapeutic range in dogs: 100 to 400 ng/ml). It should be noted that if clorazepate is given in conjunction with phenobarbital, a higher dose of clorazepate may be needed.

**MONITORING**

Because specific dosing information is not available for very young animals that require anticonvulsant therapy, careful monitoring of antiepileptic serum levels is critical. Patients should be monitored for clinical signs of toxicosis, such as excessive sedation or ataxia. Careful attention should be given to the patient’s weight and the milligram per kilogram dosing of antiepileptics.

Because changes in drug disposition in pediatric patients are difficult to predict compared with those in adult patients, therapeutic monitoring of antiepileptics is critical to ensure that effective but safe drug concentrations are maintained. Therapeutic drug monitoring should be performed when steady state has been achieved or a dose is changed. Serum levels should be evaluated if breakthrough seizures occur or signs of toxicosis are present. Monitoring can also identify compliance difficulties. Drug concentrations can be used to adjust the dose if a patient’s size changes.

As pediatric patients physiologically become adults, monitoring should continue as doses are modified in response to age-related changes in drug disposition. However, monitoring is also critical in rapidly growing animals, particularly in large-breed dogs in which weight gain is rapid and dramatic. Care should be taken to weigh patients frequently to maintain the dose on a milligram per kilogram basis. Thus pediatric patients should generally be monitored on a monthly basis for 3 to 6 months or until they become adult sized.

Therapeutic drug monitoring can be used to adjust doses of both phenobarbital and bromide. The timing of the sample is unimportant in most cases. Suggested serum level reference ranges for dogs are 15 to 40 µg/ml for phenobarbital, 100 to 200 µg/dl for bromide with phenobarbital, and 200 to 300 µg/dl for bromide alone. Although no large studies have been conducted in cats, a serum phenobarbital level of 20 to 30 µg/dl in cats has been suggested.

**EMERGENCIES**

Rapid elimination of status epilepticus is imperative because it can be life threatening. In general, the accepted form of therapy in dogs and cats is diazepam (0.5 mg/kg IV). Intranasal or rectal administration is an alternative route for antiepileptics in dogs. Longer lasting seizure therapy may need to be administered concurrently using a drug such as phenobarbital (2 to 5 mg/kg IV).

An infusion of benzodiazepines may be effective in cases of status epilepticus or cluster seizures in dogs and cats. Constant-rate infusion (CRI) of diazepam has been advocated for cats with seizures. CRI of diaz-
epam has reportedly been successful in controlling human neonatal convulsions resulting from hypoxia.\textsuperscript{74} No long-term side effects were reported. Heart rate and respiratory function should be carefully monitored.\textsuperscript{74} CRI of midazolam has been administered in human neonates with poorly controlled seizures. The most significant side effect was hypotension, which required isotropic drug administration.

In an emergency, it is important to stop seizures. This is done most effectively via intravenous doses of an anticonvulsant with a rapid onset of action. Diazepam administered at a dose of 0.5 mg/kg IV is effective. If venous access is not possible, diazepam may be given rectally at a dose of 1 mg/kg. An intraosseous catheter may be placed instead of a venous catheter. For fluid or drug administration via an intraosseous catheter, an 18- or 20-gauge needle should be used. A spinal needle with a stylet or an intraosseous needle may be used. This should be placed through the trochanteric fossa of the proximal femur.\textsuperscript{75} Alternate sites include the tibial tuberosity, greater tubercle of the humerus, or wing of the ilium.\textsuperscript{75} Intraperitoneal fluid administration has been described.\textsuperscript{79}

Other considerations for neonates with seizures include monitoring blood glucose, body temperature, and hydration status. A normal body temperature of 95°F to 99°F (35°C to 37.2°C) should be maintained. Recommended fluids are isotonic crystalloid solutions (0.45% NaCl with 2.5% dextrose). Using warm fluids to maintain body temperature is recommended. The maintenance fluid rate for neonates is 60 to 180 ml/kg/day.\textsuperscript{75} Glucose can be given orally at a dose of 1 to 2 ml of 5% to 15% dextrose.\textsuperscript{75} If an animal is hypoglycemic, 0.25 ml/25 g of 20% dextrose IV or IO should be administered.\textsuperscript{75}

**REFRACTORY CASES**

Refractory epilepsy is unsatisfactory seizure control when serum anticonvulsant concentrations are in the therapeutic range or there are unacceptable drug side effects. Treatment failures may result for many reasons. The first category is misdiagnosis; for example, a patient is not really experiencing seizures or there has not been a chance to identify (through additional diagnostics) and correct the underlying cause of seizures.\textsuperscript{81} Treatment errors may also account for poor seizure management\textsuperscript{84}; examples include poor drug choice, incorrect drug dose or interval, and lack of owner compliance. Therapeutic monitoring of anticonvulsants may identify problems with compliance or an inadequate dose.

Once it has been determined that first-line anticonvulsant therapy will not be adequate, other drug choices may be considered. Although these drugs are effective in some cases, general disadvantages include substantial cost and lack of long-term drug safety information.

Additional anticonvulsants administered in adult dogs include gabapentin, levetiracetam, felbamate, and zonisamide. A detailed review of administering these drugs in dogs can be found elsewhere.\textsuperscript{83}

**Zonisamide**

Zonisamide is a sulfonamide antiepileptic. It has been shown to be effective in controlling seizures in a small group of adult dogs with refractory idiopathic epilepsy.\textsuperscript{82} Of 12 dogs that were evaluated, 58% had significantly reduced seizure frequency when zonisamide was administered in conjunction with other anticonvulsants.\textsuperscript{76} These dogs received a mean dose of 8.9 mg/kg PO q12h.\textsuperscript{76} Zonisamide has been evaluated for long-term toxicity in dogs and was found to be safe at recommended doses.\textsuperscript{77} This drug is completely absorbed in dogs.\textsuperscript{79} It is predominately eliminated in urine.\textsuperscript{78} Erythrocytes show uptake of this drug in dogs, which could have an impact on drug disposition in young dogs because the packed cell volume of erythrocytes can be as low as 28% in 3-week-old puppies.\textsuperscript{78,79}

A suggested starting dose of this drug is 10 mg/kg PO q12h in dogs receiving phenobarbital or 5 mg/kg PO q12h in dogs not receiving phenobarbital. Zonisamide may be used as an add-on therapy or as a monotherapeutic agent.\textsuperscript{83,76} Therapeutic monitoring of trough levels using human therapeutic ranges for this drug have been suggested (10 to 40 µg/ml), although another report suggested a more narrow range of 20 to 30 µg/ml.\textsuperscript{83,80} Side effects of this drug include sedation, ataxia, and vomiting.\textsuperscript{76} Multiple reports confirm that zonisamide is an effective anticonvulsant for a variety of seizure disorders in children.\textsuperscript{81–83}

**Gabapentin**

Gabapentin is a newer anticonvulsant that may be considered for administration in young dogs and cats. The drug has an approximately 80% bioavailability in dogs and minimal protein binding.\textsuperscript{84} Approximately one-third (34%) of the drug is metabolized to N-methylgabapentin in dogs, which is different than in other species.\textsuperscript{84,85} Gabapentin does not induce hepatic cytochrome P-450. The drug also has linear elimination pharmacokinetics, which do not
change after multiple doses in dogs. The elimination half-life of gabapentin is 3 to 4 hours in dogs. It is eliminated by the kidneys. Gabapentin is available in a liquid formulation, which allows easier dose adjustment. There is no information on the clinical administration of this drug in young dogs and cats. Expected side effects of gabapentin include lethargy and ataxia. This drug is indicated as an adjunctive antiepileptic. It reportedly causes only mild side effects such as sedation. Anecdotally, it is not very effective for managing seizures in dogs.

A recommended canine dose is 25 to 60 mg/kg/day PO divided q6–8h. An initial dose of 10 mg/kg PO q8h has been suggested. In younger animals, a larger volume of distribution may lead to more rapid clearance of this drug. Gabapentin administration has been evaluated in children. A larger dose of gabapentin is needed to reach therapeutic levels in children, and there is variability in plasma concentrations of the drug that are effective in children.

**Levetiracetam**

Levetiracetam has been used as an adjunctive antiepileptic for uncontrolled seizures in dogs and appears to have pharmacokinetics that may be favorable in young dogs. This drug has a high absorption rate and does not bind to plasma proteins. Levetiracetam is poorly metabolized: Approximately 89% of the drug is excreted unchanged in the urine. The half-life after intravenous dosing in dogs is about 3.6 hours. Limited information is available regarding clinical administration of this drug in dogs; however, the drug was shown to be effective in a small group (i.e., 15) of dogs when added to phenobarbital or bromide therapy. In this study, the dose ranged from 7 to 24 mg/kg PO q8h. A suggested dose is 20 mg/kg PO q8h, with dose increases of 20 mg/kg until the drug is effective or causes side effects. The drug reportedly has minimal side effects at reported doses; however, it is expensive. Levetiracetam administration appears to be safe and effective in children. There are a few anecdotal reports of administration of this drug in cats.

**Felbamate**

Felbamate has been shown to be effective in some dogs with seizures. This drug has favorable pharmacokinetics in adult dogs. It is completely absorbed when administered orally in dogs. The half-life of felbamate in plasma is 4.1 to 4.5 hours in dogs. Felbamate is not highly protein bound in dogs. Felbamate is metabolized to multiple metabolites by the liver and then mainly excreted in the urine but partially eliminated in feces. Felbamate has been evaluated in adult dogs and may increase liver weight and serum enzymes. It may also decrease appetite and cause weight loss.

Felbamate has been evaluated in 4- to 6-week-old dogs. The drug has a lower bioavailability in young dogs than in adult dogs and a fast rate of elimination. Another study found a higher rate of metabolism in pediatric dogs given felbamate. The volume of distribution was not different than that in adult dogs, but administering a higher dose of felbamate in young dogs compared with that in adults has been suggested. Felbamate has not been clinically evaluated for seizure control in puppies; however, it has been effective in children with seizure disorders. This drug does not cause sedation. However, it has been associated with very severe complications in humans, including blood dyscrasia and hepatic dysfunction. In humans, aplastic anemia is a major concern with felbamate administration; however, it has never been reported in a child younger than 13 years of age. The risk of hepatotoxicity is also low in children. A suggested starting dose in dogs is 15 mg/kg PO q8h; however, this drug may be difficult to administer because puppies have a higher metabolism.

**DISCONTINUING ANTICONVULSANT THERAPY**

Anticonvulsant therapy may eventually be discontinued in some patients; however, if an underlying disease such as a structural brain disease (e.g., secondary to head trauma) or idiopathic epilepsy is suspected, antiepileptics may be required for life. In patients considered to be in remission and that remain seizure free for some time, seizure therapy may be discontinued. Recurrence of seizures is probably due to underlying disease. Because of physiologic dependence, it is important not to discontinue anticonvulsant therapy abruptly. Information regarding when antiepileptic therapy can be stopped is unavailable for dogs and cats. It has been suggested that therapy can be stopped after 6 months to 2 years without seizures.

**SPECIFIC THERAPY**

The underlying disease, if known, should be treated. Therapy for pediatric humans with seizures is similar to that for adult animals. It is important to realize that the underlying cause of seizures may be different. Idiopathic epilepsy is less likely in juvenile (i.e., 12 weeks to 6 months of age) dogs and unlikely in cats. Furthermore,
it is important to address the underlying disease process when it can be identified. Certain diseases require specific therapy; for example, a portosystemic shunt for surgical management with shunt ligation or medical treatment through dietary modification and antibiotic therapy may be the optimal form of therapy. Antiepileptic drug therapy should be used to stop seizures and when seizures are expected to recur, such as when an underlying cause is identified (e.g., head trauma) or when other diseases have been ruled out.

**HYPOGLYCEMIA**

Neonates exhibiting neurologic signs should receive glucose parenterally by the intravenous or intraosseous route at a dose of 0.25 ml/25 g of 10% to 20% dextrose solution. Juvenile hypoglycemia can occur because of immature hepatic enzyme systems, lack of glycogen stores, and an increased glucose requirement. Fatty liver syndrome may cause hypoglycemia in toy breed puppies at 4 to 16 weeks of age. Glucose replacement therapy involves 1 to 2 ml/kg of a 10% to 20% dextrose solution (intravenous or intraosseous) in patients that are obtunded or having seizures.

**HYDROCEPHALUS**

Medical therapy can reduce the severity of clinical signs, presumably by altering CSF production. Medical therapy may include administration of prednisone (0.25 to 0.5 mg/kg PO q12 to 24h), furosemide (0.5 to 2 mg/kg PO q12 to 24h), or acetazolamide (0.1 mg/kg PO q8h). The goal of surgical management is to shunt CSF from the ventricles to another space (e.g., atrium, abdominal cavity). Shunting procedures are the mainstay of therapy for hydrocephalus in human medicine and have become advocated in veterinary medicine. Currently used systems include the Phoenix Accura Standard Shunt System (Phoenix Biomedical Corp., Valley Forge, PA) or the Codman Uni-Shunt with Reservoir Kit (Codman and Shurtleff, Inc., Raynham, MA). Complications of shunting procedures include obstruction and shunt-related infections.

**REFERENCES**


3. What is the mechanism for bromide elimination?
   a. renal excretion
   b. hepatic biotransformation
   c. biliary clearance
   d. a combination of hepatic and renal metabolism

4. Which of the following is not a major concern for drug disposition alteration regarding anticonvulsant administration in neonates?
   a. increased volume of distribution
   b. less body fat
   c. immature liver function
   d. immature renal function

5. Bromide elimination may be influenced by
   a. diet
   b. stress
   c. seizure frequency
   d. liver dysfunction

6. Which statement regarding diazepam administration is not true?
   a. It may be useful in controlling seizures in cats.
   b. It has been associated with an idiosyncratic reaction in cats.
   c. Dogs become refractory to it for seizure control.
   d. It is the drug of choice for long-term seizure control in puppies.

7. Which drug is probably not an acceptable add-on anticonvulsant?
   a. primidone
   b. gabapentin
   c. zonisamide
   d. levetiracetam

8. In cases of hydrocephalus, which drug does not alter CSF production?
   a. prednisone
   b. furosemide
   c. acetazolamide
   d. mannitol

9. Which statement regarding discontinuation of anticonvulsant therapy is true?
   a. Drug therapy should not be stopped abruptly.
   b. Treatment may be stopped if there have been no seizures in the past 3 weeks.
   c. Diazepam should be administered daily as drug therapy is discontinued.
   d. Drug therapy may be discontinued in cats if they have been seizure free for 2 weeks.

10. As the only anticonvulsant administered to dogs, phenobarbital is considered to adequately control seizures in _______ of dogs.
   a. 20% to 30%
   b. 50% to 80%
   c. 60% to 90%
   d. 95% to 100%

### ARTICLE #4 CE TEST

This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers may purchase individual CE tests or sign up for our annual CE program. Those who wish to apply this credit to fulfill state relicensure requirements must consult their respective state authorities regarding the applicability of this program. To participate, fill out the test form inserted at the end of this issue or take CE tests online and get real-time scores at [CompendiumVet.com](http://www.CompendiumVet.com).

1. Which route of administration is not acceptable for diazepam?
   a. intraosseous
   b. transdermal
   c. intravenous
   d. rectal

2. At what age can an adult dosing scheme be used for anticonvulsants?
   a. 1 year
   b. 9 months
   c. 9 weeks
   d. 3 months

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