Timely Topics in Nutrition

Nutritional management of idiopathic epilepsy in dogs

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Idiopathic epilepsy is a condition defined by chronic, nonprogressive, recurrent seizures not attributable to other specific neurologic abnormalities. Several nutritional strategies have been proposed to help control seizures in epileptic canine patients; however, research supporting these nutritional strategies is often lacking. Epileptic dogs may also have concurrent diseases or be at risk of complications caused by medications; these factors can be addressed by use of a comprehensive nutritional management plan. In addition, the effect of nutrient-drug interactions as well as the impacts of body composition and dietary consistency on the pharmacokinetics of commonly used therapeutic compounds should be considered.

Ketogenic Diets

Ketogenic diets have been used to treat intractable epilepsy in humans. A ketogenic diet is a high-fat, adequate-protein, low-carbohydrate, calorie-restricted diet that mimics the acetonemia (ketosis) created by starvation. Classically, it has a fat-to-combined carbohydrate and protein ratio of 4:1 or 3:1 (weight basis) that provides only 75% to 80% of daily caloric requirements. The fat is typically from plant oils (long-chain PUFAs) or of animal origin (saturated fat from dairy sources to maintain palatability); however, an alternative type of ketogenic diet includes medium-chain triglycerides, which are more ketogenic than are PUFAs. In these investigations,6 and dogs do not easily become ketotic, which may be the result of efficient peripheral utilization of ketone bodies.7,8 The administration of ketone body precursors to induce circulating ketosis in dogs has not been successful because the precursors apparently are quickly utilized within a few hours after administration.9 In a small 6-month clinical trial in epileptic dogs that were receiving anticonvulsant medications, the group fed a ketogenic diet had significantly higher serum concentrations of β-hydroxybutyrate.4 The difference in β-hydroxybutyrate concentration failed to yield a significant reduction in seizure frequency, compared with the seizure frequency of the control group, because one-third of the dogs in each group had a reduction in seizure frequency of ≥ 50%. After completion of that trial, it was determined that the number of dogs in each group was insufficient for assessment of differences in seizure frequency, so it remains unclear why both groups had a reduction in seizure frequency and whether the dietary treatment had a positive effect.

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>DM</td>
<td>Dry matter</td>
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<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
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<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acid</td>
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in humans consuming ketogenic diets is a separate predictor of positive response (reduced seizure frequency) to these diets.1 In addition, there is interest in the use of increased intake of PUFAs from both the omega-3 and omega-6 series because they may provide a novel anticonvulsant mechanism by promoting ketosis as well as modulating neuronal excitability and affecting neurotransmitter synthesis through several mechanisms.1,9

Ketogenic diets can be effective in humans, with one-third of patients having a reduction in seizures of > 90% and one-third of patients having a reduction in seizures of 30% to 90%. However, they are extremely restrictive diets and not without multiple potential adverse effects and complications as well as concerns regarding compliance. Thus, ketogenic diets are reserved for patients with severe epilepsy who fail to respond to traditional treatment, and alternative less-restrictive dietary interventions are an area of active research.

The possible efficacy of ketogenic diets remains unknown in canine patients. Rodents are usually used in these investigations,2 and dogs do not easily become ketogenic, which may be the result of efficient peripheral utilization of ketone bodies.7,8 The administration of ketone body precursors to induce circulating ketosis in dogs has not been successful because the precursors apparently are quickly utilized within a few hours after administration.9 In a small 6-month clinical trial in epileptic dogs that were receiving anticonvulsant medications, the group fed a ketogenic diet had significantly higher serum concentrations of β-hydroxybutyrate.4 The difference in β-hydroxybutyrate concentration failed to yield a significant reduction in seizure frequency, compared with the seizure frequency of the control group, because one-third of the dogs in each group had a reduction in seizure frequency of ≥ 50%. After completion of that trial, it was determined that the number of dogs in each group was insufficient for assessment of differences in seizure frequency, so it remains unclear why both groups had a reduction in seizure frequency and whether the dietary treatment had a positive effect.
Other Considerations for Use of Ketogenic Diets

Although ketogenic diets remain an unproven strategy for use in dogs, they are not without potential complications and are restrictive such that it may be difficult to ensure owner compliance. Similar to other restrictive diets, ketogenic diets have been associated with essential nutrient deficiencies (eg, hypomagnesemia, osteopenia from hypovitaminosis D, or hypoproteinemia from inadequate protein consumption) in humans, and there is evidence of altered micronutrient requirements caused by shifts in energy substrates. For dogs, any long-term diet should supply adequate amounts of all essential nutrients (including protein, given that dogs have a higher requirement than do humans), and dogs consuming restrictive diets should be monitored for signs of deficiencies. As an additional consideration, ketogenic diets are high in fat (classically at least 80% to 90% of energy from fat, which exceeds the National Research Council safe upper limit for adult dogs). High-fat diets may be of concern because of the association between hypertriglyceridemia and phenobarbital treatment. In a study conducted to evaluate the efficacy of adding gabapentin to the treatment regimen of 17 dogs with seizure disorders treated with phenobarbital or phenobarbital plus bromide, mean fasting triglyceride concentrations remained increased at >3 times the upper limit of the reference range. In another study, 57 dogs treated for epilepsy had significantly higher fasting serum triglyceride concentrations, compared with concentrations for 57 healthy control dogs, but only 19 of 57 (33%) epileptic dogs had values that exceeded the range of concentrations for the control dogs. There was no difference in fasting serum triglyceride concentrations between groups of dogs receiving phenobarbital or phenobarbital plus bromide. Investigators in that study also found that 3 epileptic dogs had severe fasting hypertriglyceridemia after treatment with phenobarbital was initiated; in 2 of those dogs, the fasting serum triglyceride concentration had been within the reference limits prior to initiation of treatment, whereas there was no pretreatment measurement for the other dog. Hypertriglyceridemia may be common in epileptic dogs treated with phenobarbital, and the associated risk of pancreatitis should also be considered when initiating feeding of high-fat diets. Risk of developing pancreatitis may be increased with epilepsy, and the use of potassium bromide or phenobarbital (or both) has been implicated in the development of pancreatitis. Because the onset of clinical signs of pancreatitis can follow ingestion of fatty foods, caution should be used for implementation of dietary management plans involving a ketogenic diet, especially in dogs with other existing risk factors for pancreatitis (eg, obesity).

Other Effects of Dietary Macronutrient Distribution

Dietary macronutrient distribution (ie, the proportion of calories from protein, fat, and carbohydrate) has been implicated as a factor that affects the pharmacokinetics of phenobarbital. Investigators in 1 study reported the effects of diet on the pharmacokinetics of phenobarbital in healthy Beagles fed 3 commercial diets in sequence. They found that the half-life of phenobarbital was reduced when the dogs were fed diets with reduced protein (34 g/1,000 kcal) or with reduced fat and increased fiber (27 and 52 g/1,000 kcal, respectively), compared with the half-life when the dogs were fed the baseline diet (48 g of protein/1,000 kcal, 46 g of fat/1,000 kcal, and 5 g of crude fiber/1,000 kcal). Body weight and energy intake were not different for the dogs after consuming each diet for 2 months, but body fat (measured with dual-energy x-ray absorptiometry) was reduced after the dogs consumed the diet that was lower in both fat and protein. Diets used in the study were not controlled; they differed in macronutrient profile, fiber type and concentration, micronutrient concentrations, ingredients, and probably many other factors. This makes it difficult to interpret the findings with regard to effects of specific dietary factors. However, analysis of results of that study suggests that diet and body composition may play a role in pharmacokinetics of phenobarbital, and more research is needed.

Effect of Body Composition

The estimated volume of distribution of drugs may be impacted (to various degrees) by obesity, and guidelines differ with regard to the use of ideal versus actual body weight for the calculation of doses in human medicine. Similarly, the impact of moderate to severe muscle wasting likely also affects pharmacokinetics of certain drugs; however, scientific support for dosage adjustment is lacking in both the human and veterinary medical literature. Considering the increasing rates of obesity in many human populations, there is surprisingly little information available about the need for adjustments in phenobarbital dosages for obese humans with epilepsy, and to our knowledge, there is no information about this topic for obese dogs with epilepsy. Authors of 1 case report in humans suggest that actual body weight should be used when determining loading doses of phenobarbital for IV administration to obese patients, but information regarding the effects of body composition on maintenance dosing is lacking. The impacts of obesity on glomerular filtration rate and cardiac output likely also affect the pharmacokinetics of phenobarbital and many other drugs including levetiracetam and zonisamide, which are primarily excreted via the kidneys.

In addition, lipid solubility is a major factor in distribution of a drug in the body. Pharmaceuticals with small volumes of distribution and low lipid solubility (eg, levetiracetam) may be less affected by excess adipose tissue or muscle atrophy resulting from cachexia or sarcopenia, compared with the effects on pharmaceuticals with larger volumes of distribution resulting from binding to muscle or distribution into body fat. Regardless, the importance of maintaining an ideal body condition and stable body weight should be emphasized to owners of dogs receiving treatment for epilepsy because of the need for reliability and consistency of medication dosing as well as the association of ideal body condition with increased life span and delayed onset of other chronic disease.
Effect of Urine pH and Lithogenic Risk Factors

Urine pH is an important factor that influences the rate of excretion of various drugs. Investigators in 1 study reported that urinary alkalization with potassium citrate (administered to 5 healthy Beagles given a single dose of phenobarbital orally) resulted in an increase in the amount of phenobarbital excreted into the urine and a shorter elimination half-life, compared with results when the dogs were given ammonium chloride to acidify the urine. This may be an important consideration for patients in which epilepsy is controlled with phenobarbital and may also require alterations in dietary management or medications for the prevention or treatment of certain types of urolithiasis. The management of urolithiasis often includes alkalization or acidification of urine to discourage urolith formation or encourage urolith dissolution. In addition, for humans consuming ketogenic diets, calcium oxalate nephrolithiasis is a known complication that is hypothesized to be attributable to chronic acidosis, dehydration, and fat malabsorption. More research is needed to characterize the relationship between anticonvulsant treatment, diet, and risk of urolithiasis in veterinary patients with epilepsy.

Bromide Treatment and Dietary Considerations

Bromide, a halide, appears to cross neuronal chloride channels more readily than does chloride, and this facilitates the action of inhibitory neurotransmitters. Bromide administration for 2 to 3 weeks is required to achieve therapeutic concentrations; steady-state concentrations are achieved after approximately 3 to 4 months of administration. It is recommended that a clinician measure serum bromide concentrations at 1 and 3 months after treatment initiation to monitor the dosing regimen. It can require at least 3 months to again reach steady-state concentrations after the bromide dose is changed.

Although bromide replaces chloride throughout the body, the sum of these 2 halides remains constant. The appropriate dose of bromide depends on concurrent use of anticonvulsants (eg, phenobarbital), diet, and renal function. Bromide is excreted unchanged by the kidneys; it is freely filtered by the glomeruli and then undergoes tubular reabsorption in competition with chloride. Dietary chloride concentration and intake are key variables that affect the elimination half-life of bromide.

High-chloride diets (1.3% chloride DM) significantly shorten the elimination half-life of bromide. The predicted mean ± SD daily dose of bromide needed to maintain serum concentrations within the therapeutic range for dogs fed 1.3% chloride DM (43 ± 13 mg/kg) was almost twice as high as the dose estimated for dogs fed 0.4% chloride DM (22 ± 3 mg/kg). Use of a high-chloride diet (increased from 0.48% chloride DM to 1.18% chloride DM) has also been associated with decreased serum bromide concentrations and loss of seizure control. Conversely, toxic concentrations of bromide (bromism) can accumulate rapidly when chloride intake is decreased in patients receiving bromide.

Reversible neurologic signs are the most commonly reported signs of toxicosis in dogs treated with potassium bromide; sedation and ataxia associated with bromism can be quite profound.

In a study on the effects of chloride content on bromide elimination, a sample of 11 commercial dry dog foods had chloride contents that ranged from 0.33% to 1.32% (DM basis). Dog foods typically contain 1.0 to 2.0 g of chloride/1,000 kcal, with a range of 0.5 to 3.6 g of chloride/1,000 kcal; however, high-salt diets may contain 5.5 g of chloride/1,000 kcal. Values for chloride concentrations are not always available for commercial diets, and these do not necessarily correlate with the sodium or potassium content of a diet, which limits extrapolation. It may be necessary to avoid low chloride concentrations in diets for dogs treated with bromide to reduce the impact of daily variability or dietary indiscretion (eg, the proportion of any additional chloride is lower when the overall dietary intake is higher). However, efficacy of feeding diets with moderate versus low chloride concentrations to help maintain seizure control in dogs treated with bromide has not been clinically evaluated.

In addition to the dietary concentration of chloride, the variability of intake is also an important factor. Breakthrough seizures can be associated with abrupt dietary changes or dietary indiscretion involving foods or treats with added chloride. and bromism can occur when the dietary chloride content is abruptly reduced. Because epileptic patients may be receiving multiple medications, potential variation of chloride content in any additional foods used to administer medications should also be considered. The need for monitoring and dietary consistency should be stressed to owners of epileptic canine patients that are receiving bromide treatment.

Role of Allergic Disease

Food allergy has been proposed as a suspected cause of seizure disorders in companion animals and humans; however, the hypothesis currently lacks strong scientific support. The hypothesis is based primarily on anecdotal and uncontrolled, subjective observational information from clinical reports and case series. However, epidemiological studies in humans have indicated an association between epilepsy and allergic disease. Investigators in 1 epidemiological study found an association between epilepsy and asthma in adults. Additionally, in a recent epidemiological study of childhood epilepsy, it was reported that the odds of diagnosis of epilepsy increased with increasing prevalence of allergic diseases, including atopy, asthma, and food allergy, with further increased risk of developing epilepsy linked to more severe allergy and a higher number of allergic diseases.

Although associations between epilepsy and food allergy have been reported in humans, potential mechanisms remain elusive. Studies must be conducted to confirm a link between epilepsy and allergic disease in companion animals and to characterize any causative relationships. Currently, there is no basis for presuming that food allergy has a role in the development of epilepsy in dogs, however, there is no harm in appropriately performing a dietary elimination-rechallenge trial in an epileptic patient, assuming the owner can achieve adequate compliance, particularly if there are concur-
rent signs (dermatitis or gastrointestinal tract signs) that support a diagnosis of possible food allergy.

**Impact of Other Nutrients**

In addition to the dearth of published studies on the impact of dietary modification for dogs with epilepsy, there is also a notable lack of information regarding the effect of dietary supplementation with specific nutrients. Some of these nutrients may be of benefit in the management of animals with epilepsy, and in particular, there has been interest in the use of omega-3 fatty acids and taurine.

**Omega-3 fatty acids**—In recent years, there has been interest in the health benefits for the long-chain omega-3 PUFAs EPA and DHA. In particular, DHA has been found to play an essential role in brain development. Furthermore, omega-3 PUFAs support neuroprotection in epileptic rats, and it has been suggested that long-term administration of omega-3 PUFAs may be a treatment option for dogs with epilepsy. The mechanism of action remains unclear, but information for rodents suggests that epileptic seizures trigger an inflammatory response with increases in prostaglandins, cytokines, and reactive oxygen species. It has been postulated that acute positive effects of dietary supplementation with omega-3 PUFAs could be attributable to both anti-inflammatory effects and ion channel modifications, whereas long-term positive effects may be related to enhanced effects of γ-aminobutyric acid on transmission and neurogenesis. In 1 case report, the administration of fish oil at 2 g/d to a 2-year-old female Great Dane successfully decreased the frequency of epileptic seizures. Unfortunately, the authors of that case report did not provide an explanation for the chosen dose, nor did they provide details on the type of fish oil used or the specific DHA and EPA concentrations. In contrast, a clinical trial in 15 epileptic dogs conducted with a crossover design and a dose of approximately 115 mg of EPA plus DHA/(kg of body weight) failed to provide benefits with regard to a reduction in seizure frequency or severity during a 12-week period. Additional studies are needed to define the potential role of omega-3 PUFAs in the treatment of dogs with epilepsy, and guidelines for appropriate dosing should be developed.

In addition to postulated antiseizure effects, omega-3 PUFAs may be useful in addressing hypertriglycerideremia that sometimes develops in dogs receiving long-term treatment with phenobarbital. Although the mechanism is unclear, phenobarbital may increase hepatic production of very low-density lipoproteins. 

**Taurine**—Taurine has inconsistent, and sometimes weak, anticonvulsant properties in rodents, cats, and dogs with experimentally induced seizures and in human seizure patients. The mechanism is unclear, but it may be related to suppression of glutamate-induced toxicity, cytoprotective effects related to attenuation of bystander cell death, and support of neural development within the subventricular zone (even in adult brains). Oral and parenteral administration of taurine has reportedly been used successfully in the treatment of a small number of cats with naturally occurring epilepsy. Authors of a case series of 5 cats with epilepsy reported that twice-daily oral administration of 500 mg of taurine plus an unknown amount of pyridoxine resulted in improvement or resolution of seizures and electroencephalogram activity without concurrent use of antiepileptic medications. In another case report, use of taurine (300 mg, SC, q 12 h for 2 days, followed by 100 mg, PO, q 24 h) was associated with repeatable improvement of both seizure frequency and electroencephalogram activity in 1 epileptic cat. Plasma and whole blood concentrations of taurine were not assessed in either of those reports. To the authors’ knowledge, there are no reports of the use of taurine treatment in epileptic dogs; however, taurine is one of several amino acids with altered proportions in CSF of epileptic purpose-bred dogs, compared with the proportions in CSF of seizure-free siblings. Large clinical trials are needed to further evaluate the efficacy of taurine as a potential treatment option.

**Clinical Summary**

Anticonvulsant medications remain the cornerstone of treatment for dogs with epilepsy. Although nutritional approaches in general, and ketogenic diets in particular, play an important role in the management of epilepsy in humans, similar guidelines for dogs currently lack strong scientific support. Clinical trials are being conducted to evaluate the efficacy of a commercially available diet for use in management of epilepsy in dogs; however, details regarding the nutritional profile and other features of that diet are unknown. Regardless, the effect of diet on the success of anticonvulsant treatment is an important consideration when implementing comprehensive dietary management plans for dogs with epilepsy because of evidence for the positive impact of a consistent diet, an effect of dietary chloride content on bromide metabolism, the potential effect of macronutrient distribution on phenobarbital pharmacokinetics, and the potential neuroprotective effects of omega-3 PUFAs. In addition, alterations in nutritional profiles may help reduce the risk of associated comorbidities such as pancreatitis.

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**References**


