Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs

Dawn Merton Boothe, DVM, PhD, DACVIM, DACVCP; Curtis Dewey, DVM, MS, DACVS, DACVIM; David Mark Carpenter, PhD

Objective—To compare efficacy and safety of treatment with phenobarbital or bromide as the first-choice antiepileptic drug (AED) in dogs.

Design—Double-blinded, randomized, parallel, clinical trial.

Animals—46 AED-naïve dogs with naturally occurring epilepsy.

Procedures—Study inclusion was based on age, history, findings on physical and neurologic examinations, and clinico-pathologic test results. For either phenobarbital treatment (21 dogs) or bromide treatment (25), a 7-day loading dose period was initiated along with a maintenance dose, which was adjusted on the basis of monthly monitoring. Efficacy and safety outcomes were compared between times (baseline and study end [generally 6 months]) and between drugs.

Results—Phenobarbital treatment resulted in eradication of seizures (17/20 [85%]) significantly more often than did bromide (12/23 [52%]); phenobarbital treatment also resulted in a greater percentage decrease in seizure duration (88 ± 34%), compared with bromide (49 ± 75%). Seizure activity worsened in 3 bromide-treated dogs only. In dogs with seizure eradication, mean ± SD serum phenobarbital concentration was 25 ± 6 µg/mL (phenobarbital dosage, 4.1 ± 1.1 mg/kg [1.9 ± 0.5 mg/lb], PO, q 12 h) and mean serum bromide concentration was 1.8 ± 0.6 mg/mL (bromide dosage, 31 ± 11 mg/kg [14 ± 5 mg/lb], PO, q 12 h). Ataxia, lethargy, and polydipsia were greater at 1 month for phenobarbital-treated dogs; vomiting was greater for bromide-treated dogs at 1 month and study end.

Conclusions and Clinical Relevance—Both phenobarbital and bromide were reasonable first-choice AEDs for dogs, but phenobarbital was more effective and better tolerated during the first 6 months of treatment. (J Am Vet Med Assoc 2012;240:1073–1083)

Since the early 1990s, bromide (most commonly administered as a potassium salt) has been used as an AED for the long-term management of epilepsy in dogs. Increasingly, it is considered as an alternative to phenobarbital as the first-choice sole AED used for long-term control of epilepsy in dogs.

Successful use of both phenobarbital and bromide is facilitated by a long elimination half-life, which minimizes fluctuation in drug concentrations during a 12-hour dosing interval. Therapeutic drug monitoring is widely available and is supported by canine (rather than human) therapeutic ranges as follows: serum phenobarbital concentrations of 15 to 45 µg/mL and serum bromide concentrations of 1 to 3 mg/mL (when used as a sole treatment).

<table>
<thead>
<tr>
<th>ABBREVIATIONS</th>
<th>AED</th>
<th>Antiepileptic drug</th>
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<tr>
<td>CI</td>
<td>CI</td>
<td>Confidence interval</td>
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</table>

Each drug has its disadvantages. Both are associated with polyuria, polydipsia, and polyphagia and the sequelae associated with general sedation (eg, lethargy and ataxia), adverse effects to which an animal may develop tolerance. In addition, each has unique characteristics that complicate successful treatment. Long-term phenobarbital treatment has been associated with hepatotoxicity, although a cause-and-effect relationship has not been proven. Phenobarbital also has been associated with unpredictable, idiosyncratic adverse drug reactions, including pancytopenia and drug interactions that reflect induction of selected hepatic drug-metabolizing enzymes that target xenobiotics as well as endogenous compounds. Induction of its own metabolism might result in a decrease in plasma drug concentrations and therapeutic failure. In contrast, although renal excretion of bromide limits hepatotoxicity or induction of hepatic enzymes, its elimination half-life in dogs is so long that several months of treatment must occur with each change in dosage before steady-state concentrations (and thus maximum effect) are reached. Although this delay can be overcome by administration...
of a loading dose that targets steady-state serum bromide concentrations, such an approach also increases the risk of adverse effects, the most common of which is vomiting.\textsuperscript{5,6,11,35,36} Although drug interactions are limited with bromide, dietary chloride content predictably and proportionately impacts bromide clearance and thus plasma drug concentrations.\textsuperscript{33,35} Both phenobarbital and bromide continue to be used as first-choice AEDs,\textsuperscript{5,7} yet no studies have compared their use as drugs for control of epilepsy in dogs. The purpose of the study reported here was to compare efficacy and safety of bromide with those of phenobarbital in dogs with spontaneously occurring epilepsy.

**Materials and Methods**

This study was implemented in client-owned AED-naïve dogs with spontaneous epilepsy. Informed consent was obtained and the protocol was approved by the Clinical Research Committee of the Texas Veterinary Teaching Hospital. A sample size of 25 dogs/group was targeted to allow detection of a 40% difference in number of seizures per month between groups with a power of 80%. Patients were solicited for participation through advertisements in selected veterinary journals and through the therapeutic drug monitoring service at the Texas Veterinary Medical Center. Evaluation at Texas A&M University was not necessary for a patient to participate in the study.

**Patient selection**—Diagnosis of epilepsy was made on the basis of clinicopathologic test results, history, and findings on physical and neurologic examinations performed by the referring veterinarian at the time of evaluation because of seizures. Clinicopathologic tests consisted of a CBC, serum biochemical analysis, and measurements in serum of preprandial and postprandial bile acids concentrations and amylase and lipase activities. A standardized neurologic examination form and questionnaire were completed by the referring veterinarian, and a standardized questionnaire focusing on baseline seizure data was completed by the client. A criterion for candidate inclusion in the study included age of onset of disease between 0.5 and 6.5 years; age criterion for enrollment was selected on the basis of the currently described range that encompasses the emergence of idiopathic epilepsy. Inclusion criteria related to seizure activity included a seizure interval ≤ 1 month (no stipulation was made as to duration or number other than that each patient must have endured at least 2 seizures so that a baseline interval could be determined), no abnormal neurologic examination findings or abnormal neurologic behavior between seizure episodes, no prior AED treatment (other than diazepam necessary to control status epilepticus), and clinicopathologic test results within reference limits. When identifiable from baseline data, patients with secondary epilepsy, particularly that caused by infection, neoplasia, or metabolic diseases, were excluded. However, invasive (eg, CSF analysis) or expensive diagnostic tests (eg, MRI) necessary to rule out some causes of secondary epilepsy were not required for participation in the study.

**Drug administration**—Dogs enrolled into the study were assigned by random blocking (blocks of 10) to receive either phenobarbital or bromide. All study participants except the principal investigator (DMB) were blinded to AED administration. No study investigator served as the primary veterinarian for any study subject. However, the principal investigator (DMB), in consultation with the referring veterinarian and client, made all recommendations regarding changes in drug administration regimens for all patients. Recommendations subsequently were implemented by the client through the referring veterinarian.

To individualize dosage on the basis of response to treatment, drugs were prepared each month for each patient on the basis of therapeutic drug monitoring results. Phenobarbital\textsuperscript{8} was purchased as the finished product for administration. Bromide is not available as an approved drug. A bromide product is commercially available, but this product has not been subjected to premarket approval or assessment by any regulatory agency; rather, it is a manufactured, compounded product. Thus, bromide was compounded by use of a pure crystal substrate.\textsuperscript{8} Both drugs were prepared in opaque gelatin capsules,\textsuperscript{7} with the capsule size selected on the basis of the smallest size in which the calculated dose would fit. The calculated daily dose for each patient was administered in a maximum of 2 capsules. Filler was not used for either drug. All compounding was performed by a registered pharmacist with adherence to stipulations set forth in American Medicinal Drug Use Clarification Act and appropriate compliance guidelines.\textsuperscript{37,38} Drugs were identified on their labels by numeric codes. Clients were instructed to administer each drug at 12-hour intervals; the drug could be administered in food with the exception of the day before monitoring, for which food was withheld from dogs after midnight. Diets that dogs were receiving at the time of enrollment into the study were continued throughout the study period; treats were allowed as prior to enrollment.

The amount of AED administered to each patient was designed to target the low end of the therapeutic range at steady state, with dosages individualized for each patient on the basis of therapeutic drug monitoring.\textsuperscript{7,12–17} The elimination half-life for phenobarbital (33 to 96 hours)\textsuperscript{39,40} is considerably shorter than that for bromide (range, 15 ± 9 days to 69 ± 22 days, depending in part on chloride intake).\textsuperscript{11,33,34} To circumvent the differences in time to steady state and thus maximum efficacy for comparison between the 2 drugs, a loading dose was administered orally over a 7-day period (14 equal doses administered every 12 hours) such that steady-state drug concentrations that targeted the low end of the therapeutic range for each drug would be achieved for either drug by day 8. For bromide, a total loading dose of 450 mg/kg (204.5 mg/lb) was administered orally to achieve serum bromide concentrations of approximately 1.25 mg/mL.\textsuperscript{17} For phenobarbital, a loading dose was calculated by use of the following equation\textsuperscript{39,46}:

\[
D_L = \text{Target dose} \times \frac{\text{Vd}}{\text{F}}
\]

where \(D_L\) is loading dose, \(\text{Vd}\) is volume of distribution, and \(\text{F}\) is oral bioavailability. To target serum phenobarb-
bital concentrations of approximately 17 µg/mL, assuming 85% oral bioavailability and a volume of distribution of 0.65 L/kg, a total loading dose of 12 mg/kg (5.45 mg/lb) was calculated for oral administration.

The total loading dose for each drug was divided into 14 equal doses and administered every 12 hours over a 7-day period along with the maintenance dose. Administration of maintenance doses began on day 1 for bromide (15 mg/kg [6.8 mg/lb], PO, q 12 h) or phenobarbital (3.5 mg/kg [1.6 mg/lb], PO, q 12 h). On day 8 of treatment for either group, blood samples were obtained to monitor the serum concentration (peak at 5 hours for phenobarbital and trough for both phenobarbital and bromide) of each drug achieved with the loading dose. Also on day 8, the dosage for each drug was decreased to a maintenance dose. Serum drug concentrations were monitored again 3 weeks later (month 1) after the loading dose was completed to make sure serum drug concentrations were being maintained. If the 8-day and 3-week serum drug concentrations were not similar, the dosage was adjusted on the basis of patient response and the difference in serum drug concentrations. Thus, in general, by month 1 of treatment, a target serum drug concentration and dosage had been established for each patient. Blood samples were obtained from dogs for monitoring monthly thereafter, and adjustments were made by the investigator as described.

The target serum drug concentration for each patient was the lowest possible concentration associated with eradication of seizures (≥ 50% reduction in seizures being an acceptable second goal) and absence of intolerable adverse effects. The maintenance dose was decreased if seizures were well controlled and adverse effects were found. The dosage also was decreased for some patients for which seizures were not controlled (ie, the patient remained seizure free through 2 prestudy seizure intervals), even if adverse effects were not present, if the serum concentration of the drug was considered higher than necessary to control seizures (ie, concentrations were in the mid to high population therapeutic range). All decreases in dosage were made in 25% decrements. The targeted concentration for a patient was increased in the event that seizures were not controlled and adverse effects were either absent or tolerable. For such patients, serum drug concentrations were increased by approximately 25% by administration of a reduced loading dose and an increase in the maintenance dose. A decreased total loading dose for bromide was 200 to 250 mg/kg (91 to 114 mg/lb) and 3 to 3.5 mg/kg (1.36 to 1.6 mg/lb) for phenobarbital. The new total loading dose was divided into 6 equal doses and administered every 12 hours over a 3-day period along with the new maintenance dosage. This stepwise approach to increasing serum drug concentrations was implemented repetitively in any patient that continued to have seizures until either seizures were acceptably controlled or intolerable adverse effects emerged and persisted. Because of the concern of phenobarbital-induced hepatotoxicity, the dosage of phenobarbital was not increased any further in patients for which serum phenobarbital concentration was approximately 32 µg/mL (an additional 25% increase in phenobarbital concentrations would result in serum phenobarbital concentration ≥ 40 µg/mL). Cases in which patients continued to have seizures despite serum phenobarbital concentration ≥ 32 µg/mL were thus considered failures, and those patients were withdrawn from the study at that point. Serum bromide concentrations could reach or exceed 3 mg/mL as long as unacceptable adverse effects did not emerge. For either drug, cases in which patients were having seizures and adverse effects were unacceptable and were thus considered therapeutic failures, regardless of serum drug concentrations, and those patients were withdrawn from the study at that point.

After each monthly follow-up evaluation and 1 week prior to the next follow-up evaluation, a 6-week supply of the appropriate AED at the previous or new dosage was mailed to the referring veterinarian. During each monthly visit to the referring veterinarian, any AED not administered to the dog by its owner during the previous month was returned by the owner to the veterinarian who, in turn, returned the AED to the principal investigators. Client compliance was verified by random checks (counting) of remaining drug and by monthly therapeutic drug monitoring.

Data collection—Clients maintained a calendar and log that required daily entries regarding their dog’s response to treatment. These were sent to the client through the veterinarian at least 6 weeks prior to the start of the study, when such a delay in the implementation of treatment was acceptable to owner and veterinarian; otherwise, clients provided baseline data for the 30 days prior to study enrollment on the basis of records or the history as provided to the referring veterinarian. The calendar directed clients to mark each day either yes or no if they observed abnormal activity, including seizures, in their dog. A yes designation required a follow-up description on the log of the abnormal activity, including the time of day the activity occurred and, for seizures, the number, duration, and severity. Clients also were specifically directed to document daily any activity that might be indicative of adverse effects, including a yes or no designation for lethargy (defined as sleepiness or apathy), ataxia (described as wobbliness), appetite increase or decrease, vomiting or diarrhea, increased urination or water intake, or hyperactivity.

Patients were reevaluated by their referring veterinarian at the end of each month of treatment. Veterinarians were sent the new month’s packet containing forms and tubes for collection of blood and a new month’s supply of the AED (at the previous month’s dosage) at least 1 week prior to the monthly follow-up evaluation. Evaluation was accomplished by use of investigator-supplied standardized forms that addressed questions specifically relating to response (including evidence of adverse drug events or adverse effects) to AED treatment. Additionally, blood samples were collected for clinico-pathologic tests (as collected at baseline) and therapeutic drug monitoring. Food was withheld from dogs the night before the scheduled visit. Clients were instructed not to give the morning dose of AED and to deliver their dog to the referring veterinarian by the time the morning dose was due to be given. At the time of arrival at the clinic, a preprandial blood
sample was collected for clinicopathologic testing and determination of the trough serum drug concentration. The morning dose of AED was then administered, and 5 hours later, a peak serum drug concentration was measured. The dog was then fed, and a postprandial serum bile acids concentration was determined 2 hours later. During each reevaluation, clients submitted to the veterinarian completed monthly logs and calendars and any unused drug. Blood samples, unused drug, patient calendar and logs, and the referring veterinarian’s assessment were mailed to the principal investigator by use of a prepaid, overnight courier service. After analysis and evaluation by the study investigator, if a new drug dosage was indicated, a 6-week supply of the drug at the new dosage was immediately mailed to the referring veterinarian such that it was received within 1 week after the last follow-up evaluation and at least 3 weeks before the next follow-up evaluation. At the time of each dog’s completion of the study, the code for each drug was revealed to the referring veterinarian and client. Clinicopathologic testing and therapeutic drug monitoring results for the last month of the study and a 6-week supply of drug were provided. As an additional incentive for participation, therapeutic drug monitoring services through the investigator’s laboratory were offered at a 50% discount.

Criteria for withdrawal from the study—Withdrawal from the study could be either dog owner or investigator driven. Clients could withdraw their dog from the study at any time for any reason. Investigator-driven withdrawals occurred if clients or veterinarians failed to return daily logs, calendars, and unused drug or failed to submit the dog for monthly blood sample collection. Emergence of unacceptable adverse drug events also was a condition of withdrawal or study end as determined by communication between the owner, referring veterinarian, and principal investigator. Inclusion of data for withdrawn patients depended on the reasons for withdrawal and the time of the withdraw-

Data analysis—Phenobarbital was assayed in serum with an automated polarized immunofluorescence assay. 

\[
1/2 = 0.693/k_{\text{el}}
\]

where \(t_{1/2}\) is disappearance half-life and \(k_{\text{el}}\) is the disappearance rate constant, calculated as \(\ln \left(\frac{\text{peak}}{\text{trough}}\right)/12\) h. 

Efficacy outcome measures—At the end of the study for each dog, efficacy of each drug in controlling seizures was evaluated via several outcome measures. Seizure activity was measured as the duration (minutes) of each seizure episode (by use of a mean duration for all seizures that occurred in the month of report), number of seizures in 1 month, and duration of time (days) that lapsed between seizure episodes (seizure interval) at baseline and for the last month of the study. For dogs in which seizures were eradicated (ie, seizure interval > 180 days at study end), the number of days since the last seizure was recorded at study end (eg, 180 days if the patient did have a seizure throughout the 6-month period). Additionally, for each dog at baseline and at study end, severity of seizure activity was scored such that 0 indicated no seizure activity; 1 indicated partial motor seizures with or without altered consciousness; 2 indicated generalized tonic clonic seizures ≤ 3 minutes in duration, with or without loss of consciousness, and with only a single seizure during a 24-hour period; 3 indicated generalized tonic clonic seizures > 3 minutes, with or without loss of consciousness, defecation, urination, and vocalization, and with seizures as frequent as 2 in a 30-minute period, and 4 indicated generalized tonic clonic seizures with loss of consciousness and clustering. Clustering was defined as ≥ 3 seizures with < 30 minutes elapsing between seizures. Clients in conjunction with referring veterinarians and the principal investigator (DMB) determined the score for each patient. Finally, at study end, response to each AED was designated for each dog as eradication (0 seizures at month 6), > 50% reduction in seizure number, no response (≤ 50% decrease in seizure number), or worsening of seizure activity (an increase of any magnitude in seizure numbers at study end vs baseline). These data, along with safety data, were used to designate treatment in each dog as either a success or failure in regard to AED treatment.

Safety and adverse effects outcome measures—Clinicopathologic test data were evaluated monthly for evidence of covert illness. Hepatotoxicity, rather than induction of hepatic enzymes, was considered to be present if serum alkaline phosphatase activity and serum alanine aminotransaminase activity were ≥ 2 and 3 times, respectively, the reference range activities. In contrast, evidence of hepatic dysfunction was determined on the basis of changes in hepatic function tests (albumin,
Each patient was Forty-six patients were enrolled of at least 3 of the 4 hepatic function tests were outside of the reference range at study end. Adverse effects (eg, vomiting or diarrhea; lethargy; ataxia; polyuria, polydipsia, or polyphagia; or hyperactivity) were quantitated at baseline and month 6 by counting the number of days that the adverse effect was documented by the client as occurring in the patient during that month. In addition, the percentage of dogs that developed adverse effects (yes or no) was determined for each treatment group at months 1 and 6 (or study end) and throughout the study. For percentages, a dog was considered to have had an adverse effect regardless of the number of episodes during that month (eg, a dog that vomited once during the month was treated the same as a dog that vomited 10 times during the month).

Overall success versus failure—Each patient was designated as either a success or a failure in regard to treatment. Success was defined as > 50% reduction in the number of seizures, a severity score ≤ 2, and the lack of unacceptable adverse effects as defined by the client or referring veterinarian. Adverse effects designated as unacceptable must have been sufficiently severe to lead to patient withdrawal from the study prior to the end of the 6-month study period (including during the loading period) or cause the client to choose an alternative anticonvulsant at study end.

Statistical analysis—Descriptive data analysis included generation of mean ± SD for continuous data (clinicopathologic test results, body weight, drug dosage, and serum drug concentrations) for each time (baseline and study end) for each treatment group. An exception was for disappearance half-life, which was reported as the harmonic mean and pseudo-SD. Median and range were determined for nonparametric data, including categorical data (seizure severity scores) or data that were not normally distributed (seizure efficacy and adverse effects).

Data analysis established the efficacy and safety of each drug by comparing responses at study end to baseline seizure activity within groups. Nonparametric variables were compared between times via the Wilcoxon signed rank test, whereas continuous variables were compared between times via a paired Student t test. For phenobarbital, comparisons were also made for disappearance half-life after initial loading period (7 days) and at study end by use of a paired t test. Values of P ≤ 0.05 were considered significant for all comparisons.

Data analysis also compared the efficacy at study end and safety at study beginning (month 1) and between the 2 drugs. Analysis of variance could not be performed on nonparametric data, which included most of the efficacy data and adverse effects safety data. Thus, for efficacy comparisons between drugs, percentage change of study-end data from baseline data was compared via the Wilcoxon rank sum test. For continuous, normally distributed data, comparisons were made at study end between drugs via a Student t test for either equal or unequal variance as appropriate for each parameter. The proportion of dogs with each degree of seizure severity was compared between groups at baseline and study end by means of χ² analysis. Additionally, the proportion of dogs for which seizure activity was eradicated and the proportion of dogs for which AED treatment was considered a success were compared between treatment groups by means of χ² analysis. For adverse effects, χ² analysis was also used to compare the number of dogs with a specific adverse effect at month 1, throughout the study (total), and at study end.

Results

Study animals—Forty-six patients were enrolled in the study: 21 in the phenobarbital group and 25 in the bromide group. The study included 7 mixed-breed dogs, 5 Labrador Retrievers, 3 Golden Retrievers, 3 Miniature Schnauzers, 3 Standard Poodles, 2 Welsh Springer Spaniels, 2 Siberian Huskies, 2 Greyhounds, 2 German Shepherd Dogs, 2 Dalmatians, 2 Collies, and 1 each of the following dogs: Basset Hound, Beagle, Bichon Frise, Border Collie, Cocker Spaniel, Dachshund, English Springer Spaniel, German Shorthaired Pointer, Italian Greyhound, Miniature Dachshund, Pug, Rottweiler, and Schnauzer. Male dogs were disproportionately represented; there were 11 sexually intact males, 4 sexually intact females, 21 castrated males, and 10 spayed females. Seizures in the majority (33/46 [72%]) of patients were scored at baseline as either 4 (17/46 [37%]) or 3 (16/46 [35%]) in severity. At baseline, severity of seizures for bromide-treated dogs was less than that of phenobarbital-treated dogs. The proportion of dogs with a seizure severity score of 2 at baseline was significantly (P = 0.005) lower in phenobarbital-treated dogs (1/21 [4.8%]), compared with bromide-treated dogs (7/25 [28%]). Although the proportion of patients at baseline with scores of 3 or 4 was 86% (18/21) for phenobarbital-treated dogs and 60% (15/25) for bromide-treated dogs, these proportions did not differ significantly. Groups did not differ significantly in terms of sex (phenobarbital-treated dogs, 14/21 [67%] males and 7/21 [33%] females; bromide-treated dogs, 18/25 [72%] males and 7/25 [28%] females), body weight (phenobarbital-treated dogs, mean ± SD of 22.7 ± 13 kg [49.9 ± 28.4 lb]; bromide-treated dogs, mean ± SD of 22.8 ± 11.5 kg [50.2 ± 25.3 lb] and median of 23 kg [50.6 lb]), or age (phenobarbital-treated dogs, mean ± SD of 3.3 ± 1.7 years and median of 3 years; bromide-treated dogs, mean ± SD of 3.1 ± 1.5 years and median of 3 years).

Twenty of 21 phenobarbital-treated dogs and 23 of 25 bromide-treated dogs completed the study (indicating both safety and efficacy could be evaluated); the power to detect a 40% change in seizures per month was decreased from the target of 80% to 70%. One dog in the phenobarbital group ingested 1 month’s supply of phenobarbital on day 7. This patient was treated supportive and was discharged 3 days after ingestion with no adverse events; the owner chose to withdraw the dog from the study. All data on this patient other than baseline and safety (prior to accidental ingestion) were excluded from data analysis, and this patient was considered neither a...
failure nor a success. Treatment of this patient was continued by administration of bromide with no adverse effects. For the bromide group, 2 dogs were withdrawn from the study at day 7 (during the loading period) because of an unacceptable adverse effect (ie, vomiting). Because duration of treatment was < 2 months, efficacy data were not available for these dogs. However, safety data were included; furthermore, both dogs were considered failures. Month 6 was not the final month (study end) for all dogs. One dog in the phenobarbital group was withdrawn from the study at month 2 because of the development of neutropenia (not present at month 1); month 2 data were considered as study-end data for this dog. All data were included for this patient; despite the fact that the dog had responded to treatment (seizures eradicated), it was considered a failure because of the unacceptable adverse effect. Noncompliance (failure to bring dogs to monthly follow-up examinations) led to investigator-directed completion at month 3 for 1 phenobarbital-treated patient and at month 2 for 1 bromide-treated patient. The failure to bring these dogs to follow-up examinations was unrelated to either drug safety or efficacy for these dogs. Data collected at the respective month of withdrawal for each dog were considered as study-end data for these 2 dogs, and their data were included. In all, study withdrawal occurred in 1 phenobarbital-treated dog and 2 bromide-treated dogs (at day 7) and study end occurred prior to 6 months in 1 bromide-treated dog and 2 phenobarbital-treated dogs.

**Efficacy data**—Several efficacy measures improved at study end, compared with baseline, for both drugs (Table 1). For phenobarbital-treated dogs, seizure number (P = 0.001), duration (P = 0.001), and severity (P = 0.001) were significantly decreased and seizure interval was significantly (P = 0.001) increased at study end, compared with baseline. For bromide-treated dogs, seizure number (P = 0.005) and severity (P = 0.001) were significantly decreased and seizure interval was significantly (P = 0.001) increased at study end, compared with baseline; seizure duration decreased over time, although not significantly (P = 0.08). The percentage of dogs in which seizure activity was eradicated was significantly (P < 0.001) greater for phenobarbital-treated dogs (17/20 [85%]), compared with bromide-treated dogs (12/23 [52%]). For those dogs that still had seizures at study end, the percentage decrease in seizure duration also was greater (P = 0.04) for phenobarbital-treated dogs, compared with bromide-treated dogs. The percentage of dogs in which seizures were successfully controlled was greater for phenobarbital-treated dogs (15/20 [75%]), compared with bromide-treated dogs (15/23 [65%]), albeit not significantly (P = 0.059). Insufficient numbers of dogs had seizures at study end; therefore, severity scores could not be compared between treatment groups. A seizure severity score of 0 was achieved by study end in 17 of 20 phenobarbital-treated dogs and in 12 of 23 bromide-treated dogs. Seizure activity worsened at study end, compared with baseline, in 3 of 23 (13%) bromide-treated dogs (2 dogs were 2.5 years old and 1 was 3 years old), but not in any phenobarbital-treated dogs. However, the risk of an increase in seizures with bromide treatment, compared with phenobarbital treatment, was not significant (P = 0.14).

**Drug concentrations**—Mean serum concentrations and dosages in phenobarbital-treated dogs and bromide-treated dogs at study end were summarized (Table 2). After the loading period (day 8), the mean trough serum phenobarbital concentration was 29 ± 13 µg/mL (95% CI, 23 to 34 µg/mL), whereas at month 1, the concentration was 22 ± 7.7 µg/mL (95% CI, 19 to 26 µg/mL). For those patients in which seizures were eradicated, mean phenobarbital concentration at study end was 25.4 ± 5.4 µg/mL (range, 12 to 34 µg/mL; 95% CI, 23 to 28 µg/mL). Seizures in 1 patient were > 50% controlled but not eradicated despite a serum drug concentration of 30.7 ± 6.1 µg/mL. Seizures in 2 patients did not improve at all despite drug concentrations of 35 and 36 µg/mL. The correlation between phenobarbital dosage and either treatment response or serum drug concentrations (R² = 0.242) was poor. Because changes in serum phenobarbital concentrations over time might reflect changes in drug dosage

Table 1—Comparison of seizure activity between phenobarbital-treated (n = 21) and bromide-treated (25) epileptic dogs* at baseline and study end.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PB treatment</th>
<th>KBr treatment</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>95% CI</td>
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<tr>
<td>Seizure duration (min)</td>
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<tr>
<td>Baseline</td>
<td>5.7 ± 3.2a</td>
<td>3.5–7.9</td>
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<tr>
<td>Study end</td>
<td>1.2 ± 3.6b</td>
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<tr>
<td>Change (%)</td>
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<td>Seizure interval (d)</td>
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<tr>
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<tr>
<td>Study end (d)</td>
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<tr>
<td>Change (% × 100)</td>
<td>16 ± 39c</td>
<td>0.1–32</td>
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<tr>
<td>No. of seizures/mo</td>
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<tr>
<td>Baseline</td>
<td>4.4 ± 6.3a</td>
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<tr>
<td>Study end</td>
<td>0.4 ± 0.9a</td>
<td>0.0–0.8</td>
</tr>
<tr>
<td>Change (%)</td>
<td>87 ± 32</td>
<td>13–74</td>
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*Study withdrawal occurred in 1 phenobarbital-treated dog and 2 bromide-treated dogs (at day 7), and study end occurred prior to 6 months in 1 bromide-treated dog and 2 phenobarbital-treated dogs. 
*Means with different letters were significantly (P < 0.05) different within treatment groups; for bromide-treated dogs, seizure duration decreased over time, although not significantly (P = 0.08). 
**Means with different letters were significantly (P = 0.05) different between treatment groups at that time. KBr = Potassium salt of bromide. PB = Phenobarbital.
or changes in disappearance half-life (ie, resulting from autoinduction), peak and trough serum phenobarbital concentrations were measured to calculate half-life. Blood samples to measure both peak and trough serum phenobarbital concentrations were obtained on both day 8 and month 6 for 15 of the 21 patients. Mean disappearance half-life at study end of 40 ± 31 hours (range, 14 to 120 hours; 95% CI, 29 to 56 hours) was significantly (P = 0.05%) less than that at baseline (68 ± 31 hours; 95% CI, 56 to 88 hours). The greatest decrease in half-life in a single dog was from 120 hours on day 8 to 21 hours at study end (month 6). Half-life decreased by ≥25% in 9 of 15 patients; an increase in seizure activity necessitated an increase in the phenobarbital dosage in 5 of these 9 dogs. An increase in serum phenobarbital concentration by ≥25% at study end, compared with month 1, occurred in 6 of 20 (30%) patients.

For bromide, mean serum bromide concentration after the loading period (day 8) was 1.3 ± 0.4 mg/mL (95% CI, 1.2 to 1.5 mg/mL). At month 1, the mean serum bromide concentration was 1.3 ± 0.3 mg/mL (95% CI, 1.1 to 1.5 mg/mL), indicating the maintenance dose was successful in maintaining serum concentrations achieved by loading. An increase in serum bromide concentrations at study end, compared with month 1, occurred in 52% (12/23) of patients. For those patients in which seizures were eradicated, mean serum bromide concentration was 1.8 ± 0.6 mg/mL (range, 0.9 to 3.3 mg/mL). In the 5 patients in which seizures were decreased by ≥50% but not eradicated, mean serum bromide concentration was 2.1 ± 0.6 mg/mL. In the patient in which seizures were <50% controlled, serum bromide concentration was 1.39 mg/mL; this patient became lethargic, and a further increase in the dosage of bromide was not pursued (Table 2). For the 3 dogs receiving bromide for which seizure activity worsened (as determined on the basis of number of seizures per month), serum bromide concentrations were 1.8, 2.5, and 2.9 mg/mL; the dosage of bromide could not be increased without causing unacceptable lethargy in these dogs. As with phenobarbital, the correlation between bromide dosage and either treatment response or serum drug concentrations (R² = 0.0018) was poor.

Safety and adverse-effects data—Mean ± SD body weight was significantly higher at study end, compared with month 1, for dogs in the phenobarbital group (23 ± 13 kg vs 25 ± 14 kg [50.6 ± 28.6 lb vs 55.0 ± 30.8 lb]), respectively. Of 21 phenobarbital-treated dogs, body weight increased in 12 and decreased in 2. Mean ± SD body weight was significantly higher at study end, compared with month 1, for dogs in the bromide group (23 ± 11 kg vs 24 ± 13 kg [50.6 ± 24.2 lb vs 52.8 ± 28.6 lb], respectively). Of 23 bromide-treated dogs, body weight increased in 10 and decreased in 8. Whereas percentage change in body weight did not differ between groups at study end, the percentage of dogs that lost weight was significantly (P = 0.02) greater in the bromide group, compared with that for the phenobarbital group.

The percentage of phenobarbital-treated dogs with clinical signs considered to be adverse effects at month 6 was significantly (P < 0.001) less than that for month 1 for polyuria, polydipsia, polyphagia, lethargy, and ataxia; most clinical signs were absent by month 6 (Table 3). For clinicopathologic test results of phenobarbital-treated dogs, significant differences over time included serum albumin concentration (decreased; P = 0.009) and serum alkaline phosphatase activity (increased; P < 0.001). However, despite these significant differences, mean clinicopathologic test data were within reference limits at study end for dogs in the phenobarbital group (Table 4). One dog in the phenobarbital group was withdrawn from the study at month 2 because of neutropenia with fever. The total WBC and neutrophil counts in this patient were 2,700 × 10³ WBCs/µL and 900 × 10³ neutrophils/µL, respectively; the PCV in this patient at month 2 was 44%, compared with 54% at baseline. Because of this adverse event, the patient was withdrawn from the study and treatment was switched to bromide. The WBC count was normalizing in this patient at 2 weeks following discontinuation of phenobarbital treatment.

Two patients in the bromide group were withdrawn from the study within the first 2 weeks after drug administration because of vomiting (Table 3). One dog was almost withdrawn because of hyperactivity. The percentage of dogs with clinical signs indicative of adverse effects at month 6 was significantly (P < 0.001) less than that for month 1. Mean clinicopathologic data did not differ between times and was within reference limits at all times for dogs in the bromide group.

There were no significant differences between treatment groups in clinicopathologic test results at baseline (Table 4). Significantly different percentage change in selected clinicopathologic data at study end included decreased serum albumin concentration (P = 0.02) and increased serum alkaline phosphatase activ-

### Table 2—Serum drug concentrations in phenobarbital-treated (n = 20) and bromide-treated (23) epileptic dogs*† with controlled or uncontrolled seizure activity at study end.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum PB (µg/mL)</th>
<th>Serum bromide (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of dogs (%)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>All dogs</td>
<td>20</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>100% controlled</td>
<td>17 (85)</td>
<td>25.4 ± 5.4</td>
</tr>
<tr>
<td>50% to &lt;100% controlled</td>
<td>1 (5)</td>
<td>30.7</td>
</tr>
<tr>
<td>&gt;0% to &lt;50% controlled</td>
<td>2 (10)</td>
<td>36</td>
</tr>
<tr>
<td>Worsened seizure activity</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Dogs received phenobarbital (mean ± SD, 4.11 ± 1.1 mg/kg [1.87 ± 0.5 mg/lb]; range, 3.9 to 4.9 mg/kg [1.77 to 2.32 mg/lb]) or bromide (mean ± SD, 10.9 mg/kg [13.9 ± 4.95 mg/lb]; range, 26 to 35 mg/kg [11.8 to 15.9 mg/lb]) orally twice a day.

†See Table 1 for remainder of key.
ity (P < 0.001) for the phenobarbital group, compared with the bromide group. Adverse effects for which the proportion of affected dogs was greater for the phenobarbital group, compared with the bromide group, at month 1 were polyuria, lethargy, and ataxia; this difference was significantly (P < 0.001) greater for the bromide group, compared with the phenobarbital group.

**Discussion**

This study supports preferential use of phenobarbital, compared with bromide, for the sole treatment of epilepsy in dogs. Efficacy of phenobarbital was better as determined on the basis of the higher proportion of dogs for which seizures were eradicated and the shorter duration of seizures; overall success was better, albeit not significantly (P = 0.06), for phenobarbital. The potential role of differences in drug concentrations (relative to the therapeutic range) for either drug as a reason for better efficacy comparison between treatment groups was minimized in the present study by our approach of using monitoring to guide treatment in each patient. For patients that continued to have seizures once steady-state concentrations were reached, the drug dosage (and thus serum concentration) for either drug was increased. Drug dosages continued to be increased until either seizures were controlled or the dog developed adverse effects that were considered unacceptable by the client (or the risk was considered unacceptable by the study investigator), in which case the dog was considered a failure in terms of treatment. From a safety standpoint, polyuria, lethargy, and ataxia were more common in the phenobarbital group as treatment was begun (month 1). However, after the loading period, mean serum phenobarbital concentrations (29 µg/mL; in the mid to high therapeutic range) exceeded the target (1.25 mg/mL) achieved after the loading period (1.3 mg/mL) during the loading period (1.3 mg/mL) achieved after the loading period (1.3 mg/mL) achieved after the loading period (1.3 mg/mL). Despite better improvement, by study end, mean serum phenobarbital concentrations had decreased, compared with base-

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**Table 3—Proportion of epileptic dogs with adverse effects that received either phenobarbital or bromide at 1 month, study end, and throughout the study (total).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PB (n = 20)</th>
<th>KBr (n = 23)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypnoea (%)</td>
<td>30</td>
<td>9</td>
<td>0.020</td>
</tr>
<tr>
<td>Polydipsia (%)</td>
<td>40</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Polyphagia (%)</td>
<td>30</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Lethargy (%)</td>
<td>50</td>
<td>22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ataxia (%)</td>
<td>55</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>15</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>5</td>
<td>13</td>
<td>0.040</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>30</td>
<td>35</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P value for those proportions that differed significantly (P < 0.05) between treatment groups. NS = No significant difference.

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**Table 4—Mean ± SD changes in clinicopathologic data over time in dogs with spontaneous epilepsy that were treated with either phenobarbital (n = 21) or bromide (25).**

<table>
<thead>
<tr>
<th>Variables</th>
<th>RB</th>
<th>PB</th>
<th>KBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>2.4–3.6</td>
<td>4.1 ± 0.6*</td>
<td>3.8 ± 0.8*</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>10–130</td>
<td>45 ± 22</td>
<td>47 ± 23</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>24–147</td>
<td>48 ± 30*</td>
<td>125 ± 95*</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0–0.8</td>
<td>0.3 ± 0.2</td>
<td>0.3 ± 0.4</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>5.0–29</td>
<td>16 ± 4.3</td>
<td>18.1 ± 7.7</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>120–247</td>
<td>205 ± 64</td>
<td>211 ± 53</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>0–25</td>
<td>6.5 ± 3</td>
<td>5.9 ± 2.6</td>
</tr>
<tr>
<td>PreBA (µmol/L)</td>
<td>&lt;13</td>
<td>14 ± 12.2</td>
<td>6.2 ± 2.9</td>
</tr>
<tr>
<td>PostBA (µmol/L)</td>
<td>&lt;30</td>
<td>20 ± 18.3</td>
<td>8.3 ± 12</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>37–55</td>
<td>53 ± 6.8</td>
<td>50 ± 6.8</td>
</tr>
<tr>
<td>WBC count (×10³/mL)</td>
<td>6,000–17,000</td>
<td>9,190 ± 3,639</td>
<td>8,923 ± 3,943</td>
</tr>
</tbody>
</table>

*Significantly different between times within phenobarbital group (P < 0.009 for serum albumin concentration and <0.001 for serum ALP activity). †Percentage change is significantly different between treatment groups (P < 0.02 for serum albumin concentration and <0.001 for serum ALP activity).


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See Table 2 for remainder of key.
line, but serum bromide concentrations were increased relative to baseline. Vomiting and lethargy persisted in the bromide group, compared with the phenobarbital group, at study end. Seizure activity worsened in 13% of bromide-treated dogs but no phenobarbital-treated dogs. Worsening seizures are a recognized, albeit rare, reaction to selected anticonvulsants.37 Although not a statistically significant change, the increase might nonetheless be clinically relevant. When considered together with safety data, successful control of seizures, which included both efficacy and safety data, was greater but not significantly (P = 0.06) so with phenobarbital. Nonetheless, this study does not exclude bromide as a reasonable first-choice AED for control of epilepsy in dogs; seizures were eradicated in > 50% of bromide-treated patients.

For phenobarbital, mean serum concentrations increased approximately 20% between months 1 and 6; for bromide, mean serum concentrations increased approximately 50%; these changes reflected dose increases. Yet, for both drugs, the percentage of dogs that developed adverse effects markedly decreased. As such, this study does support accommodation to the common adverse effects caused by either phenobarbital or bromide in dogs. These clinical signs were documented by the owner, and as such, it is possible that it was the owner, rather than the dog, that adapted to the adverse effects. However, veterinarians assessed patients monthly, thereby decreasing the risk of owner bias in assessment.

One adverse effect for which accommodation was less common was vomiting, which occurred more frequently in the bromide group. Hypertoncity and direct gastric irritation are likely to have contributed to these clinical signs. The risk of vomiting was likely increased by the loading approach to drug treatment; vomiting was sufficiently unacceptable in 2 dogs during the loading period that their owners requested withdrawal from the study. Both dogs were subsequently started on phenobarbital with no adverse effects. However, close to 30% of bromide-treated dogs still were vomiting at day 30 (3 weeks after the loading period) and 20% were still vomiting at study end. It is possible that vomiting may have been decreased if bromide had been administered as a sodium salt, rather than potassium salt, or as a liquid, rather than capsule. Bromide and phenobarbital have been associated with increased serum triglyceride concentration48 or pancreatitis49 in dogs, suggesting this as a possible cause of vomiting in the present study. Serum pancreatic lipase immunoreactivity has proven useful for assessing the likelihood of pancreatitis.50 However, at the time that the present study was implemented, this test was not routinely offered. Serum amylase and lipase activity remained normal, supporting but not proving the lack of pancreatitis as a cause of vomiting in the bromide-treated patients. The incidence of vomiting in dogs of the present study suggests that a loading dose with bromide be avoided if there is no need to rapidly achieve therapeutic concentrations.

For phenobarbital, the concern for liver disease caused us to not increase drug dosage further in dogs in which trough concentrations were approximately 32 µg/mL. Among the difficulties associated with phenobarbital use is discriminating phenobarbital-associated hepatotoxicity from phenobarbital-associated induction of liver enzymes.19,20 Phenobarbital, but not bromide, was associated with a mean increase in serum alkaline phosphatase activity at study end, compared with baseline. This increase may be due to induction of serum alkaline phosphatase activity (rather than liver disease) as was indicated by the lack of changes indicative of hepatic disease (ie, alanine aminotransaminase activity and BUN, serum albumin, or bile acid concentrations). However, the results of the present study can only be applied to a 6-month period and only if trough concentrations are maintained at < 36 µg/mL (the highest trough measured at month 6 in the present study). The lack of adverse effects at month 6 for phenobarbital, compared with bromide, in this study must be balanced with the potential need to monitor hepatic function tests.

Another sequela of phenobarbital-associated induction of metabolizing enzymes is the risk of drug interactions, which may have occurred in this study. Because we monitored both peak and trough serum phenobarbital each month, we were able to demonstrate a decrease in disappearance half-life in most patients receiving phenobarbital. Changes in disappearance half-life likely contributed to the poor correlation between phenobarbital dosage and either treatment response or serum phenobarbital concentration. The shortest half-life measured in any patient was 14 hours; the greatest change measured in any 1 patient was a decrease from 120 to 21 hours. For such patients, serum phenobarbital concentrations will decrease over time, increasing the risk of therapeutic failure. For the present study, a decrease in serum phenobarbital in association with a shortened half-life often required a dosage increase. Another sequela of shortened phenobarbital half-life is the potential for significant changes in peak and trough concentrations during a single dosing interval, as Levitski and Trepanier4 previously demonstrated in 9% of canine patients (n = 33) receiving phenobarbital for control of epilepsy. The greatest difference between peak and trough phenobarbital concentration occurred in the patient with a 14-hour half-life; concentrations declined from a peak of 17 to a trough of 12 µg/mL.

Because a lower serum phenobarbital concentration increases the risk of therapeutic failure, we recommend that serum phenobarbital concentration monitoring be performed on the basis of collection of a trough sample such that the lowest concentration that occurs during a dosing interval can be determined. In patients in which control is difficult, collection of both a peak and trough sample might be prudent to identify the potential role of short disappearance half-life in causing therapeutic failure.

Although previously reported therapeutic ranges for both bromide and phenobarbital are supported by the present study, we also demonstrate that the concentrations (and drug dosages) required to control seizures in dogs are quite variable. For phenobarbital, the lowest (12 µg/mL) and highest (34 µg/mL) effective serum concentrations differed by almost 3-fold. Likewise, for bromide, the lowest (0.9 mg/mL) and highest (3.3 mg/mL) serum concentrations associated with control differed almost 4-fold. This variability exemplifies the importance of therapeutic drug monitoring as a tool for guiding treatment. Monitoring allowed us to maintain...
low concentrations in patients that otherwise would have been exposed unnecessarily to higher concentrations. We also did not consider a therapeutic failure to have occurred unless serum drug concentrations were high enough to be associated with a risk of liver disease (phenobarbital) or the patient had signs of overdose (phenobarbital or bromide). Although a population therapeutic range for either phenobarbital or bromide is a reasonable target as treatment is begun, monitoring of drug concentrations and clinical signs should determine the range necessary to control seizures in individual patients. Failure should be ascribed to subtherapeutic concentrations for the patient until the patient continues to have unacceptable seizure activity despite concentrations or if unacceptable adverse effects emerge.

One of the weaknesses of this study is the lack of diagnostic procedures that would be necessary to rule in idiopathic epilepsy (a diagnosis by exclusion). Although the inclusion criteria were designed to increase the likelihood that idiopathic epilepsy was the cause of seizures in study participants, it cannot be confirmed in any patient. At the time the study was funded, MRI was not a routine option in practice, and including this as a requirement for participation would have caused logistic and financial burdens that would have precluded obtaining an adequate number of study participants. Our inclusion criteria for age ranged from 1 to 6 years (with the most likely age of onset of epilepsy being 1 to 5 years). Four study participants that met all criteria for inclusion (2 in each treatment group) were > 5 but < 6.5 years of age. For 3 of these dogs, seizures were eradicated; in the fourth (bromide), seizures were decreased in duration and number by 50% and the severity score was decreased from 4 to 3. Thus, although the seizures in these patients may be less likely to be associated with idiopathic epilepsy than were the seizures in the other patients, the inclusion of these older patients does not appear to have biased the data toward therapeutic failure.

This study demonstrates that both phenobarbital and bromide are reasonable first-choice AEDs, but phenobarbital may be more efficacious. Regarding adverse effects, phenobarbital may be more difficult to start if a loading dose is used; however, once steady-state serum concentrations are reached, adverse effects are more likely to persist for bromide. This study also suggests a poor relationship between drug dosage and serum drug concentrations, suggesting that serum drug concentrations should be monitored for guidance in adjustment of drug dosage as control is sought in epileptic dogs.

References:

38. US FDA Center for Veterinary Medicine. Chapter 6, Subchapter 600, Regist-extralabel drug use in animals; final rule, 21 CFR Part 530.

From this month’s AJVR

Effects of acepromazine maleate on platelet function assessed by use of adenosine diphosphate–activated and arachidonic acid–activated modified thromboelastography in healthy dogs
Bobbi J. Conner et al

Objective—to evaluate the effect of acepromazine maleate administered IV on platelet function assessed in healthy dogs by use of a modified thromboelastography assay.

Animals—6 healthy adult mixed-breed dogs.

Procedures—Dogs received each of 3 treatments (saline [0.9% NaCl] solution [1 to 2 mL, IV] and acepromazine maleate [0.05 and 0.1 mg/kg, IV]) in a randomized crossover study with a minimum 3-day washout period between treatments. From each dog, blood samples were collected via jugular venipuncture immediately before and 30 and 240 minutes after administration of each treatment. A modified thromboelastography assay, consisting of citrated kaolin–activated (baseline assessment), reptilase-ADP–activated (ADP-activated), and reptilase-arachidonic acid (AA)–activated (AA-activated) thromboelastography was performed for each sample. Platelet inhibition was evaluated by as-sessing the percentage change in maximum amplitude for ADP-activated or AA-activated samples compared with baseline values. Percentage change in maximum amplitude data were analyzed by use of Skillings-Mack tests with significance accepted at a family-wise error rate of P<0.05 by use of Bonferroni corrections for multiple comparisons.

Results—No significant differences were found in the percentage change of maximum amplitude from baseline for ADP-activated or AA-activated samples among treatments at any time.

Conclusions and Clinical Relevance—Platelet function in dogs, as assessed by use of a modified thromboelastography assay, was not inhibited by acepromazine at doses of 0.05 or 0.1 mg/kg, IV. This was in contrast to previous reports in which it was suggested that acepromazine may alter platelet function via inhibition of ADP and AA. (Am J Vet Res 2012;73:595–601)