Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992–1996)

Lauren A. Trepanier, DVM, PhD; Andrea Van Schoick, BS; Wayne S. Schwark, DVM, PhD; Joseph Carrillo, DVM

Objective—To determine therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide.

Design—Retrospective study.

Animals—122 dogs with major motor epilepsy.

Procedure—Medical histories were collected for epileptic dogs treated with potassium bromide with or without phenobarbital sodium or primidone, from which serum was submitted for bromide analysis from May 1992 to May 1996 to the Therapeutic Drug Monitoring Program at Cornell University’s College of Veterinary Medicine. A therapeutic response (improved seizure control) was defined as a ≥ 50% reduction in seizure frequency following initiation of bromide treatment. Serum bromide and phenobarbital concentrations and therapeutic outcome were determined for all dogs.

Results—72% of epileptic dogs had a ≥ 50% reduction in seizure frequency following initiation of treatment with potassium bromide. Discontinuation of barbiturate treatment was possible in 19% of those dogs originally treated with phenobarbital or primidone. Of those dogs continued on bromide and phenobarbital, 45% maintained seizure control with serum phenobarbital concentrations < 20 μg/ml. Significantly higher serum bromide concentrations were required when dogs were initially or eventually treated with bromide alone (mean bromide concentration, 1,906 μg/ml) compared with dogs treated with potassium bromide along with a barbiturate (mean bromide concentration, 1,621 μg/ml).

Clinical Implications—When dogs are treated with bromide and phenobarbital, a reasonable therapeutic range for serum bromide concentrations is 810 to 2,400 μg/ml, and for bromide treatment alone, the range is 880 to 3,000 μg/ml. When phenobarbital is used in combination with bromide, a reasonable therapeutic range for serum phenobarbital concentrations is 9 to 36 μg/ml, although in some dogs treated with bromide, phenobarbital can eventually be discontinued. (J Am Vet Med Assoc 1998;213:1449–1453)

Seizures are estimated to affect approximately 3% of all dogs, with 10 to 50% of epileptic dogs having seizures that are refractory to phenobarbital sodium alone.13 Bromide is a halide anticonvulsant that offers an effective alternative to phenobarbital and other barbiturates for treatment of epilepsy in dogs.3 Bromide reduces the frequency, severity, and intensity of seizure episodes in dogs with refractory seizures.7 Potassium bromide is commonly administered in combination with phenobarbital, but is also gaining popularity as a single agent for first-line treatment of epilepsy in dogs.8

Bromide treatment is often initiated in epileptic dogs in response to development of unacceptable adverse effects during high-dose phenobarbital treatment, such as behavior changes or liver toxicosis. The goal of bromide treatment in these dogs is to reduce or discontinue the dosage of phenobarbital while maintaining seizure control. Although results of one study7 indicated a mean reduction of 32% in phenobarbital dosage during bromide treatment, it is not clear how many dogs can eventually be taken off of phenobarbital completely. It is also not clear whether targeting higher serum bromide concentrations will facilitate discontinuation of phenobarbital.

Monitoring serum phenobarbital concentrations is important for management of epileptic dogs on phenobarbital because seizure control in dogs correlates best with serum phenobarbital concentrations, not with the administered dose of phenobarbital.3 The therapeutic range for serum phenobarbital concentrations in dogs treated with phenobarbital alone is well established.20 However, the accepted therapeutic range for phenobarbital may not apply to dogs being treated with pheno-barbital and bromide, and the therapeutic range for phenobarbital in dogs on combination treatment has not been evaluated.

Like serum phenobarbital concentrations, measurement of serum bromide concentrations is also important for management of epileptic dogs treated with bromide. Serum bromide concentrations can vary for a given dose, because elimination of bromide varies with renal function1 and chloride content in the diet.6,9 A therapeutic range for serum bromide concentrations of 1,000 to 2,000 μg/ml has been extrapolated from human studies and has been used as a target range for dogs treated with bromide and phenobarbital in combination.7 When bromide is used as a single agent, higher serum concentrations of bromide appear to be necessary to control seizures.3 However, the optimal target range for serum bromide concentrations in dogs on bromide treatment alone has not been established.

The purpose of the study reported here was to...
determine therapeutic serum anticonvulsant concentrations in treated epileptic dogs. More specifically, in epileptic dogs treated with bromide, we wanted to determine the overall efficacy of bromide in reducing seizure frequency, the percentage of dogs for which bromide treatment allows a reduction or discontinuation of phenobarbital treatment, the range of serum phenobarbital concentrations maintained in bromide-treated dogs with satisfactory seizure control, whether this range is the same as the therapeutic range established for phenobarbital treatment alone, and the range of serum bromide concentrations that control seizures in dogs treated with bromide alone or in combination with phenobarbital. In addition, we wanted to determine whether high serum bromide concentrations increase the chance of eventually discontinuing phenobarbital treatment, and whether high serum bromide concentrations are associated with better seizure control.

Criteria for Selection of Cases

Medical histories were obtained from referring veterinarians and owners of epileptic dogs for which serum was submitted for bromide analysis to the Therapeutic Drug Monitoring program at the College of Veterinary Medicine at Cornell University between May 1992 and May 1996. These epileptic dogs included those referred to the Veterinary Medical Teaching Hospital at Cornell as well as epileptic dogs treated with potassium bromide in private practices throughout the United States. The following criteria were used for inclusion in the study: availability of an adequate history (body weight, drug dosages, record of observed seizure events prior to and following bromide initiation, diet history), presence of major motor (grand mal) seizures (ie, dogs with only psychomotor or focal seizures were excluded), a documented pattern of seizures during phenobarbital treatment and prior to initiation of bromide (ie, dogs for which bromide and phenobarbital treatment was started at the same time, and dogs for which bromide was initiated after the first seizure or cluster of seizures, were excluded), availability of serum samples submitted at the time of steady state equilibrium (at least 2 weeks on the same dosage of phenobarbital, and at least 4 months on the same dosage of bromide and on the same diet), and the availability of at least 4 months of follow-up after the initiation of bromide treatment.

Procedures

Seizure numbers were tabulated as the total number of observed seizures, normalized to the number of seizures per month. Seizures were counted for the entire period prior to bromide initiation during which the dosage of phenobarbital was unchanged and barbiturate treatment was at steady state. For the period following bromide initiation, seizures were counted for the entire period during which the dosage of bromide and the diet were unchanged, and serum bromide concentrations were at steady state, through to the time of last follow-up. For the purposes of this study, individual seizures in a cluster were counted as separate seizure events. A successful response (improved seizure control) was defined as ≥ 50% reduction in the number of seizures per month without a perceived increase in the severity (intensity or estimated duration) of individual seizures.

Serum bromide concentrations were determined by a modified gold colorimetric method as previously described. Serum phenobarbital concentrations were determined by use of a fluorescence polarization immunoassay. Samples that were submitted in serum separator tubes for phenobarbital analysis were excluded from the study to avoid spuriously low phenobarbital concentrations that have been associated with the use of these tubes.

Statistical analysis—Serum drug concentrations were expressed as mean ± SD. Percentages were expressed directly with 95% confidence intervals (CI), using a table of confidence limits for proportions. For comparisons of serum drug concentrations between groups, an unpaired t-test was used, with a set at 0.05 (one-tail). For comparison of serum drug concentrations among multiple groups, a one-way ANOVA was used, followed by a Fisher’s protected least significant difference test. For comparisons of proportions, a χ² test was used. All statistics were performed by use of a commercial statistics program.

Results

Of 143 dogs for which serum was submitted for bromide analysis between May 1992 and May 1996, 122 dogs were included in the study (Table 1) on the basis of the criteria for selection of cases. One hundred and nine dogs were started on bromide treatment because of seizures that were considered by the referring veterinarian to be refractory to phenobarbital or primidone; 6 dogs were treated with bromide as a first-line agent; and 7 dogs had no seizures on phenobarbital or primidone but began bromide treatment because

Table 1—Treatment categories of epileptic dogs for which serum was submitted for bromide analysis from May 1992 to May 1996

<table>
<thead>
<tr>
<th>Treatment categories</th>
<th>No. of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital and bromide</td>
<td></td>
</tr>
<tr>
<td>Dogs with improved seizure control (mean ± SD seizure reduction 84 ±18%)</td>
<td>12</td>
</tr>
<tr>
<td>Phenobarbital dosage increased</td>
<td>16</td>
</tr>
<tr>
<td>Phenobarbital dosage unchanged</td>
<td>37</td>
</tr>
<tr>
<td>Phenobarbital dosage decreased</td>
<td></td>
</tr>
<tr>
<td>Dogs with inadequate seizure control (&lt; 50% seizure reduction)</td>
<td>24</td>
</tr>
<tr>
<td>Bromide alone</td>
<td></td>
</tr>
<tr>
<td>Dogs with improved seizure control (mean seizure reduction, 90 ± 20%)</td>
<td>18</td>
</tr>
<tr>
<td>Phenobarbital discontinued</td>
<td>5</td>
</tr>
<tr>
<td>Never on phenobarbital</td>
<td>2</td>
</tr>
<tr>
<td>Dogs with inadequate seizure control (&lt; 50% seizure reduction)</td>
<td>1</td>
</tr>
<tr>
<td>Phenobarbital discontinued</td>
<td>7</td>
</tr>
<tr>
<td>Never on phenobarbital</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>122</td>
</tr>
</tbody>
</table>

* Bromide treatment was initiated to allow a dosage reduction of primidone or phenobarbital because of adverse effects attributed to barbiturates. All of these dogs had either a dosage reduction or discontinuation of barbiturate administration with resolution of adverse effects and no subsequent observed seizures.
of adverse effects (eg, high liver enzyme activities) attributed to barbiturates.

Overall, 72% of dogs (88/122) treated with bromide had improved seizure control (≥ 50% reduction in seizure frequency compared with the period prior to bromide initiation), with a mean follow-up of 14.2 ± 4.7 months (range, 4 to 60 months; median, 12.1 months) from the time of initiation of bromide treatment. Of 116 dogs that were originally treated with phenobarbital or primidone, 22 dogs, or 19% (95% CI, 12 to 27%), were eventually taken off of barbiturate treatment and were treated successfully with bromide alone, while maintaining improved seizure control. For an additional 40 of 116 dogs (34%; 95% CI, 25 to 44%) with improved seizure control, the dosage of phenobarbital was reduced by a mean of 47% (range, 6 to 84%).

For dogs (n = 65) with improved seizure control that were maintained on some phenobarbital or primidone treatment in combination with bromide treatment, the mean serum phenobarbital concentration associated with improved seizure control was 22.6 ± 11.4 μg/ml (range, 3.7 to 55.6). Although the range of serum phenobarbital concentrations was wide, the mean value was significantly lower (P = 0.002) than therapeutic concentrations reported for dogs on phenobarbital alone (mean, 27 μg/ml; recommended therapeutic range, 15 to 45 μg/ml; Fig 1). In fact, although all of these dogs on combination treatment with bromide had successful seizure control, 45% had serum phenobarbital concentrations < 20 μg/ml, whereas 27% had phenobarbital concentrations < 15 μg/ml.

Steady state serum bromide concentrations associated with seizure control in dogs treated with bromide and phenobarbital ranged rather widely, from 500 to 2,880 μg/ml, with a mean of 1,621 ± 541 μg/ml. However, a high serum bromide concentration was associated with the ability to discontinue phenobarbital treatment (Fig 2). In dogs for which phenobarbital was eventually discontinued, the mean serum bromide concentration was significantly higher (2,043 ± 792 μg/ml; range, 880 to 3,410 μg/ml) than the mean serum bromide concentrations for dogs for which the dosage of phenobarbital was decreased but not eliminated (1,657 ± 519 μg/ml range, 530 to 2,680 μg/ml) or was unchanged (1,470 ± 592 μg/ml; range, 500 to 2,570 μg/ml).

For dogs treated with bromide alone (either as a first-line agent or following discontinuation of barbiturates), the mean serum bromide concentration associated with improved seizure control was 1,906 ± 793
bromide alone required serum bromide concentrations > 2,000 µg/ml, than did dogs on combination treatment (only 26% [17/65]; \( P = 0.023 \)). Among dogs that were treated only with bromide at last follow-up, those dogs that were initially refractory to phenobarbital treatment alone had higher serum bromide requirements (2,042 ± 791 µg/ml), compared with dogs that were treated only with bromide from the onset (1,412 ± 638 µg/ml; Fig 4). However, this difference was not significant (\( P = 0.053 \)), most likely because of the small number of dogs (n = 5) initially on bromide treatment alone in this study. Finally, with respect to the efficacy of high serum bromide concentrations, a significantly greater percentage of dogs with serum bromide concentrations > 2,000 µg/ml had improved seizure control following bromide initiation (91%; 29/32), compared with those dogs with serum bromide concentrations < 2,000 µg/ml (71% [59/83]; \( P = 0.02 \)).

**Discussion**

Bromide was effective overall in improving seizure control (defined as a ≥ 50% reduction in the number of observed seizures) in 72% of epileptic dogs, most of which were considered initially refractory to treatment with barbiturates alone. These results are similar to those reported by others, in which 65% (11/17) of dogs had a ≥ 50% reduction in seizure frequency for a year or more on bromide treatment. Thus, bromide is a remarkably effective anticonvulsant in dogs. Most dogs in this study were maintained on bromide and phenobarbital, with a wide range of serum bromide concentrations. However, for most dogs treated with this combination of anticonvulsants, a reasonable therapeutic range for bromide observed in most of our improved dogs is 810 to 2,400 µg/ml. This is on the basis of the lower 10th and upper 90th percentiles, respectively, of the dogs in our study (Fig 3).

Therapeutic serum phenobarbital concentrations in dogs treated with bromide also varied widely. However, significantly lower concentrations of phenobarbital were required in dogs concurrently treated with bromide, compared with the therapeutic range established for phenobarbital treatment alone. It should be stated that while most of these samples were obtained just prior to the morning dose (ie, at trough), this was not uniform for all samples. Thus, the range of serum phenobarbital concentrations observed in this study reflects concentrations reached throughout the dosing interval.

A reasonable therapeutic range for phenobarbital in dogs also treated with bromide is 9 to 36 µg/ml. This is on the basis of the lower 10th and upper 90th percentiles, respectively, of observed phenobarbital concentrations in improved dogs (Fig 1). Thus, the lower end of the previously established therapeutic range for serum phenobarbital concentrations should not be applied to bromide-treated dogs. In addition, low serum phenobarbital concentrations alone are not an indication to increase the dosage of this drug in dogs that are also receiving bromide. In fact, the therapeutic range for serum phenobarbital concentrations in dogs also treated with bromide has no actual lower end, because some dogs can be taken off of phenobarbital...
completely following initiation of bromide treatment. Therefore, clinical response, rather than serum phenobarbital concentrations alone, should dictate the need for phenobarbital dosage adjustments.

Thirty-four percent of dogs with seizures that were initially treated with phenobarbital were able to have a reduction in the dosage of phenobarbital by a mean of 47%, even while having improved seizure control. This is important in light of the fact that dogs with phenobarbital-associated hepatotoxicity can have an improvement in clinical signs (eg, resolution of icterus and coagulopathy) when the dosage of phenobarbital is reduced, even if the drug is not completely discontinued.\(^4\)\(^5\) Indeed, in this study, the initiation of bromide and subsequent reduction in the dosage of phenobarbital was associated with a reduction in abnormal liver enzyme activities or bile acids in all of those dogs for which liver enzyme activities were measured (data not shown).

In 19\% of epileptic dogs initially treated with barbiturates, phenobarbital or primidone was completely discontinued while improved seizure control was maintained. This indicates that in some epileptic dogs, bromide can be substituted for phenobarbital as a more effective anticonvulsant. Dogs treated with bromide alone required higher serum bromide concentrations than did dogs treated with bromide in combination with phenobarbital. For dogs on bromide alone, an acceptable therapeutic range (again, on the basis of lower 10th and upper 90th percentiles of observed bromide concentrations in improved dogs) is 880 to 3,000 \(\mu\)g/ml. This is wider than the therapeutic range previously recommended by our laboratory and others.\(^6\)\(^7\)\(^8\) Despite this wide range, mean therapeutic serum bromide concentrations were > 2,000 \(\mu\)g/ml when bromide was substituted for phenobarbital. Thus, serum bromide concentrations should generally be targeted to > 2,000 \(\mu\)g/ml in epileptic dogs if discontinuation of phenobarbital is desired. In addition, there may be higher serum bromide requirements in dogs previously refractory to phenobarbital and now on bromide alone, compared with those initially treated only with bromide.

Finally, although we have proposed fairly wide therapeutic ranges for bromide when used alone or with phenobarbital, high serum bromide concentrations (> 2,000 \(\mu\)g/ml) were associated with a greater chance of improved seizure control than were low serum bromide concentrations (< 2,000 \(\mu\)g/ml). Thus, any epileptic dogs with continued seizures that are not well controlled on bromide should have their serum bromide concentrations titrated to > 2,000 \(\mu\)g/ml, with careful monitoring for adverse effects.

There are several potential biases associated with a retrospective study based on samples submitted by referring veterinarians for drug analysis. First of all, bromide treatment is often initiated in dogs on phenobarbital just following a period of worsened seizure activity, which can be followed naturally by a period of decreased seizure activity even without changes in treatment. Secondly, there is a loss of follow-up for those patients in which bromide is discontinued early in treatment (ie, before 4 months) because of poor initial response. Finally, there is an inherent bias on the part of the clinician and the client to look for improvement after a new treatment is introduced. All of these factors could falsely increase the observed efficacy of bromide. To counteract these potential biases, seizure frequencies were tabulated during the entire period that the dog was on a stable dosage of phenobarbital prior to bromide initiation, not only for the period just prior to bromide initiation. In addition, clinical improvement was defined rather stringently as a $\geq$ 50\% reduction in seizure frequency, to minimize the effects of small biases in the observed number of seizures.

\(^{4}\)Abbott Tdx, Abbott Diagnostics, Abbott Park, Ill.

References