Clinical signs, risk factors, and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy

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Objective—To evaluate clinical signs, risk factors, and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy treated with potassium or sodium bromide.

Design—Retrospective case-control study.

Animals—83 clinically ill epileptic dogs with (cases; n = 31) and without (controls; 52) bromism.

Procedures—Medical records were reviewed for information regarding signalment, epilepsy history, treatment, diet, clinicopathologic test results, concurrent diseases, clinical signs, and outcome. Case and control dogs were matched by the veterinary hospitals from which they were referred and by month of admission. A presumptive diagnosis of bromism was made in case dogs when treatment for primary clinical signs was limited to induction of diuresis or reduction in the dose of bromide administered, and this diagnosis was supported by serum bromide concentrations. Potential risk factors for bromism were identified via univariate and subsequent multivariate logistic regression analyses.

Results—Common clinical signs of bromism included alterations in consciousness, ataxia, and upper and lower motor neuron tetraparesis and paraparesis. The multivariate analysis identified bromide dose at admission to the hospital as the only factor significantly associated with bromism. In all dogs with bromism, treatment via dose reduction or facilitated renal excretion of bromide resulted in rapid clinical improvement, although breakthrough seizures happened during treatment in 8 of 31 (26%) dogs.

Conclusions and Clinical Relevance—Bromism is a clinically heterogeneous, dose-dependent neurotoxicosis that is largely reversible with treatment. Regular serial monitoring of serum bromide concentrations is recommended to optimize anticonvulsant treatment in dogs with idiopathic epilepsy. (*J Am Vet Med Assoc* 2009;234:1425–1431)

The potassium and sodium salts of bromide are reportedly effective anticonvulsants for the treatment of dogs with idiopathic epilepsy, whether administered alone or as a component of a multidrug protocol.[1–6] In dogs, bromide is a popular anticonvulsant drug because it is effective, safe, and economical; it is not a controlled substance; and its half-life allows for convenient once or twice daily administration.[3–6] The adverse effects commonly associated with bromide administration in dogs are usually mild and self-limiting or are tolerated by owners because of the perceived therapeutic benefit of bromide treatment. Such adverse effects include polyuria, polydipsia, polyphagia, ataxia, sedation, and gastric irritation[3,6] and may be potentiated in dogs concurrently receiving other anticonvulsant medications, particularly phenobarbital.[3,4] In addition, these bromide-associated adverse effects can often be alleviated via dosage changes based on monitoring of serum bromide concentrations or by tailored adjustments of bromide administration schedules or practices.[1–4]

Bromide toxicosis (bromism) is the toxic condition resulting from the ingestion of excessive bromide-containing compounds, and it develops in dogs and humans treated with bromide.[7–10] In humans, bromism is a heterogeneous clinical syndrome characterized by mildly debilitating to life-threatening neuropsychiatric, dermatologic, and gastrointestinal symptoms.[10] Clinical signs attributed to bromism in dogs are predominantly neurologic and include CNS depression ranging from delirium to coma, CNS hyperexcitability, ataxia, and tetraparesis or paraparesis.[2,5,7–9] Clinical reports of bromism in dogs are uncommon. The low number of reports[5–7,11] may be attributable to a greater resistance of dogs versus humans to toxicoses, endogenous variability in bromide pharmacokinetics within individual dogs and possibly between dog breeds, or lack of reporting of dogs with bromism.

Although bromism reportedly develops in a dose-dependent manner in dogs and humans, the degree of clinical tolerance of bromide varies among recipients, and as a result, serum bromide concentrations poorly predict impending bromism, particularly in dogs.[2,3,5,7] Because bromide is primarily eliminated through the kidneys, renal insufficiency resulting in diminished

Abbreviations

LMN	Lower motor neuron
UMN	Upper motor neuron

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bromide excretion is a reported risk factor for the development of bromism in dogs receiving doses of bromide within the recommended therapeutic range.[8] Other postulated risk factors for the development of bromism in dogs include breed predispositions, comorbid neurologic disease, reduced dietary salt intake, and concurrent use of other anticonvulsant drugs.[5,7] Although the effects of variable dietary chloride concentrations on the pharmacokinetics of bromide have been described in isolated clinical reports[5,7,12] and investigated in laboratory colonies of healthy dogs,[13] none of these postulated risk factors have been evaluated in bromide-treated dogs in which idiopathic epilepsy was diagnosed. The objective of the study reported here was to evaluate clinical signs, risk factors, and outcomes associated with bromism in dogs with idiopathic epilepsy treated with potassium or sodium bromide.

Materials and Methods

Animals—A cross-referenced search of the veterinary medical record and central laboratory cost-accounting databases of the Virginia-Maryland Regional College of Veterinary Medicine Veterinary Teaching Hospital was conducted to identify all dogs for which a diagnosis of idiopathic epilepsy had been recorded from January 1996 through December 2006 and in which a serum bromide concentration had been measured during hospitalization. For inclusion in the study, all dogs were required to have been referred to the teaching hospital for evaluation of a clinical illness unrelated to seizures. All dogs were also required to have had a clinical diagnosis of idiopathic epilepsy on the basis of the following: historic evidence of first seizure between 9 months and 6 years of age, unremarkable results of prior interictal neurologic examinations, and no historic, clinical, or clinicopathologic evidence of a metabolic or toxic disorder at the time of diagnosis. Because another study[11] of dogs referred to the teaching hospital for emergency treatment of seizures or evaluation for chronically poor control of seizures revealed that subtherapeutic serum anticonvulsant concentrations were common among these dogs, dogs specifically referred for treatment of seizures were excluded from the present study in an attempt to eliminate selection bias between the case and control dogs. Dogs receiving bromide alone or in combination with other anticonvulsant drugs were candidates for inclusion.

Dogs were eligible for inclusion in the case group when a clinical diagnosis of bromism, bromide toxicosis, or bromide "toxicity" was coded in the medical record. In addition, dogs were required to have received no treatment at the teaching hospital to ameliorate the signs of bromism other than reduction of the dosage of bromide, induction of diuresis with IV administration of physiologic saline (0.9% NaCl) solution, or another treatment administered to facilitate renal excretion of bromide. Dogs were eligible for inclusion in the control group when the clinical illness that existed at the time of admission to the teaching hospital was caused by disease or diseases other than bromism and the treatment dogs received while hospitalized did not include alteration of previously prescribed anticonvulsant drugs. Case and control dogs were matched by the veterinary clinic from which the referral was made and the calendar month of the year during which each dog was admitted to the teaching hospital. Because serum bromide concentrations are not necessarily predictive of bromism in dogs,[5,7] case and control dogs were not additionally differentiated on the basis of an arbitrary value for serum bromide concentration.

Medical records review—For each dog in both groups, the primary clinical sign that was evident when dogs were admitted to the teaching hospital was recorded. For dogs that were evaluated for suspected neurologic disorders, clinical signs were classified on the basis of the site to which the neuroanatomic lesion had been localized by the attending or consulting neurologist or the neurology resident during the neurologic examination performed on the day of hospital admission. Routine examination criteria were used to assign these neuroanatomic sites. By convention, UMN disease was considered to exist when paresis, deficits in postural reactions, or both were detected in clinically affected limbs and were associated with normal to exaggerated spinal reflexes or muscle tone. On the other hand, LMN disease was considered to exist when paresis, deficits in postural reactions, or both were detected in clinically affected limbs and were associated with diminished or absent reflexes or muscle tone. The duration of clinical signs prior to hospital admission was also recorded.

Potential risk factors associated with bromism were categorized as follows: signalment, epilepsy history (including duration of idiopathic epilepsy at the time of admission), medications, diet, clinicopathologic testing results, and concurrent diseases. Medication factors included type, dosage, daily dose, and duration of all anticonvulsant drugs administered prior to admission; interval between admission and measurement of the last serum concentration of anticonvulsant drug (bromide,[a,b] phenobarbital,[c] or both); results of that last measurement; and results of the measurement obtained when dogs were admitted to the teaching hospital. When possible, data regarding alterations in the prescribed dosage of anticonvulsant drugs made within 1 year prior to admission to the teaching hospital were obtained from seizure logs maintained by dog owners or medical records from referring veterinarians. For the purposes of the study, monitoring of anticonvulsant treatment was considered suboptimal when any one of the following criteria was met: serum concentration of bromide was never monitored, and the dog received bromide for ≥ 80 days; bromide dosage was altered at the veterinarian's request without subsequent measurement of serum concentration of bromide; or the interval between serially obtained serum bromide concentrations exceeded 240 days in a dog that received a constant daily bromide dose. For other medications received prior to admission, information on the type, dosage, route, and duration of administration and reason for the prescription were included in the medication factor (concurrent medication) category.

Data on diet included the type (ie, commercial ration or homemade diet), manufacturer, brand, amount, and frequency of feeding of a dog's primary daily source of calories. For dogs that consumed commercial rations, the mean dry-matter diet-specific nutrient contents of

sodium and chloride were subsequently obtained from product literature available to veterinarians through printed or electronic resources provided by the manufacturer. Clinicopathologic variables included Hct; serum concentrations of cholesterol, bilirubin, urea nitrogen, creatinine, glucose, potassium, sodium, chloride, albumin, and globulins[d]; and serum activities of alanine aminotransferase and alkaline phosphatase.

Concurrent diseases were considered those that existed in addition to the primary disease associated with the chief clinical complaint for which the dog was referred to the teaching hospital. These data were included when substantiated by results of clinicopathologic, diagnostic imaging, histopathologic, or microbiologic evaluations and were coded on a master problem list in temporal association with the date of hospital admission.

Statistical analysis—Data were analyzed by the use of a statistical software package.[e] Summary data for continuous variables are reported as mean ± SEM. A univariate modeling procedure was used to screen all potential risk factors to identify variables that warranted additional analysis. The association between each categoric variable and bromism was assessed by use of conditional logistic regression. The associations between each continuous variable and bromism were evaluated by use of mixed-model ANOVA with the variables upon which case and control dogs had been matched treated as random effects. Factors that achieved a liberal *P* value ($P \leq 0.10$) in the univariate analyses were considered for inclusion in a final multivariate conditional logistic regression model.

Multivariate modeling was first performed by use of stepwise conditional logistic regression. Initial attempts with this approach to modeling resulted in the selection and inclusion of only serum bromide concentration at admission as an independent variable, and this variable was correlated with several other variables. Therefore, serum bromide concentration at admission was removed and stepwise conditional logistic regression was performed again. In that situation, the model algorithm selected total daily bromide dose at admission as the only significant factor associated with bromism. From clinical experience and these initial modeling attempts, it was clear that bromide dosage and serum concentration were both risk factors for the development of bromism, and ultimately, the total daily dose of bromide at admission was retained in the final multivariate model. The final multivariate model was then manually generated. Manual procedures included grouping and ranking the other variables that had been identified in univariate analyses as significantly associated with bromism on the basis of biological relationships and Pearson correlation coefficients. The groups and ranks included serum markers of renal function (creatinine and urea nitrogen), phenobarbital-related factors (serum phenobarbital concentration at admission and duration of phenobarbital treatment prior to admission), dietary factors, bromide-related factors (interval to last measurement of serum bromide concentration), serum concentrations of electrolytes (chloride and sodium), and age. The model based on bromide dose at admission was built by manually adding variables from these categories in order of rank and examining the SEMs; variables with high SEMs were eliminated. In the final multivariate model, values of $P < 0.05$ were considered significant.

Results

Animals—Medical records of 1,298 dogs with idiopathic epilepsy treated with bromide and that were admitted to the veterinary teaching hospital during the 10-year study period were reviewed. Eighty-two dogs met the inclusion criteria, including 31 dogs with bromism (2% of all dogs; case dogs) and 52 dogs with illnesses or injuries unrelated to seizures (control dogs). Thus, the prevalence of bromism in dogs with idiopathic epilepsy was 2%. Dogs included in the study were referred to the teaching hospital from 30 veterinary hospitals. There was no clear difference between case and control dogs with respect to the distribution of dog breeds. Breeds included mixed (31% [n = 26]), German Shepherd Dog (7% [6]), Labrador Retriever (6% [5]), Golden Retriever (6% [5]), Beagle (5% [4]), Jack Russell Terrier (5% [4]), Great Dane (4% [3]), Dachshund (4% [3]), Miniature Poodle (4% [3]), Standard Poodle (4% [3]), Border Collie (2% [2]), and 1 each of other pure breeds (22% [18]). The distributions of female and male dogs did not differ significantly ($P = 0.63$) between groups. Mean ± SEM body weight did not differ significantly ($P = 0.53$) between case (24.9 ± 3.1 kg [54.8 ± 6.8 lb]) and control (22.5 ± 3.1 kg [49.5 ± 6.8 lb]) dogs; however, case dogs (7.2 ± 0.5 years) were significantly ($P = 0.08$) older than control dogs (6.2 ± 0.37 years) according to the standard set for considering variables for inclusion in a multivariate model.

Signs of disease—The most common clinical signs of disease in the 52 control dogs included focal, painful UMN paraparesis or paraplegia caused by intervertebral disk disease (n = 15 [29%]), unilateral hind limb lameness (13 [25%]) resulting from cranial cruciate ligament rupture (8) or traumatic appendicular skeletal fracture (5), and weight loss, vomiting, or diarrhea (8 [15%]) resulting from nonspecific gastroenteritis (2), inflammatory bowel disease (1), hypoadrenocorticism (1), gastric adenocarcinoma (1), jejunal foreign body (1), giardiasis (1), or gastrointestinal lymphosarcoma (1). The mean duration of clinical signs for control dogs prior to referral was 15.3 ± 6.4 days.

All 31 case dogs had clinical signs attributable to neurologic dysfunction. Neurologic examinations revealed that 9 dogs had clinical signs suggestive of diffuse intracranial disease, 8 had clinical signs of UMN tetraparesis, 8 had clinical signs of UMN paraparesis, 3 had clinical signs of LMN paraparesis, 2 had clinical signs of diffuse motor neuron disease (flaccid tetraparesis), and 1 had cerebellar ataxia. Of the 9 dogs with diffuse intracranial disease, the predominant clinical sign in 7 was stupor (n = 6 dogs) or coma (1). Stupor was defined as a state of lethargy and immobility with a reduction in or inappropriate responsiveness to applied vigorous stimulation (tactile, auditory, or nociceptive). Coma was defined as the state of un-

consciousness associated with a complete lack of responsiveness to all applied stimuli. Of the 6 dogs with stupor, 3 also had bilateral mydriasis associated with slow and incomplete pupillary light reflexes. It was not possible to discern from medical records whether the mydriasis was associated with visual deficits in these 3 dogs. The clinical signs in the remaining 2 dogs with diffuse intracranial disease were head pressing and bilateral thalamocortical blindness in one and propulsive pacing and intermittent periods of aggression directed at inanimate objects in the other. All dogs with UMN tetraparesis or paraparesis were also reported as having ataxic gaits. Both dogs with diffuse motor neuron disease also had a history of regurgitation and flaccid tetraparesis, and 1 also had dysphagia. Megaesophagus was radiographically confirmed in those dogs during hospitalization. The mean duration of clinical signs prior to referral in all case dogs was 18.6 ± 7.1 days, which was not significantly different from that of the control group.

Fourteen case dogs underwent neurodiagnostic procedures (myelography, computed tomography, or magnetic resonance imaging, with or without CSF analyses) to determine the cause of the observed neurologic signs. However, results of these evaluations for all dogs were unremarkable. Both case dogs associated with diffuse motor neuron disease and megaesophagus were measured for serum titer of autoantibody against acetylcholine receptors and serum concentrations of thyroid gland hormones, and results of these tests were within respective reference ranges.

Treatment for bromism—All case dogs were treated via bromide dose reduction. The mean dosage of bromide at admission for case dogs was 44.9 ± 1.7 mg/kg/d (20.41 ± 0.77 mg/lb/d; therapeutic dose, 20 to 40 mg/kg/d [9.1 to 18.2 mg/lb/d]), and the mean initially recommended bromide dose reduction for all dogs was 12.6 ± 2.4 mg/kg/d (5.7 ± 1.1 mg/lb/d).

Four dogs with neurologic signs were treated as outpatients, and a reduction in the daily dose of bromide was prescribed. The remaining 27 were hospitalized and treated with IV administration of physiologic saline solution to induce diuresis. Five of these dogs were also treated with IV administration of furosemide (mean daily dose, 6.3 ± 0.5 mg/kg [2.9 ± 0.2 mg/lb]). Four of the dogs in which diuresis was induced had breakthrough seizures while hospitalized, all of which were successfully treated with IV administration of diazepam. None of the dogs treated with furosemide had breakthrough seizures. The mean duration of hospitalization for the 27 dogs that were hospitalized was 3.4 ± 0.7 days, and the mean serum bromide concentration at the time of discharge was 2.5 ± 0.4 mg/mL.

Outcome—Follow-up examinations or conversations with owners or referring veterinarians revealed that 26 of 29 dogs (all 4 outpatient dogs and 22 hospitalized dogs) had complete resolution of clinical signs of bromism. Additional follow-up examinations and monitoring of serum bromide concentrations were performed at the teaching hospital for 16 dogs (3 outpatient dogs and 13 hospitalized dogs). These reexaminations were generally recommended to take place at an interval of 1 bromide half-life (approx 25 days) and took place a mean of 33 ± 4 days after dogs were discharged from the teaching hospital. Clinical signs of bromism, including regurgitation in a dog with diffuse motor neuron disease, had resolved in all 16 dogs by that time. The mean time to optimal recovery in the 16 dogs reexamined at the teaching hospital was longer in the outpatient dogs (25.8 ± 3.6 days), compared with that in hospitalized dogs (7.1 ± 2.2 days). At the time of reexamination, the mean serum bromide concentration in those dogs was 2.3 ± 0.2 mg/mL.

In 4 dogs (1 outpatient dog and 3 hospitalized dogs), seizure activity increased (ie, the interictal interval decreased) between the time of discharge and reexamination. Consequently, an additional anticonvulsant was prescribed for the treatment of 3 dogs (felbamate, levetiracetam, or zonisamide). Additional reexaminations at the teaching hospital and follow-up telephone conversations with owners and referring veterinarians (mean follow-up interval, 186 ± 23 days) revealed that 22 of the 31 dogs treated for bromism did not have any relapse of clinical signs attributed to bromism.

The 3 hospitalized case dogs that did not recover completely originally had evidence of spinal cord disease (1 dog had UMN tetraparesis, and 2 had UMN paraparesis), were receiving a treatment combination of phenobarbital and bromide, and had persistent hind limb ataxia. Additional reductions in anticonvulsant drug doses were not attempted in these dogs because of owner concern that a reduction might render the drugs less effective.

Concurrent medications and disease—Sixteen (52%) case dogs and 26 (50%) control dogs were receiving various medications in addition to bromide or phenobarbital at the time of admission to the teaching hospital. Such medications included corticosteroid drugs, NSAIDS, and antimicrobials. There was no significant (P = 0.90) difference between groups with respect to the distribution of these medications. Of the 16 case dogs receiving concurrent medication at the time of admission, 14 were being treated with the medications to ameliorate clinical signs ultimately associated with bromism. Review of the medical records of 11 of the 14 dogs indicated that the owner had not perceived an impact of the additional medications on the clinical course of disease prior to referral. Medications other than anticonvulsants were specifically prescribed to ameliorate clinical signs associated with a primary disease other than idiopathic epilepsy in 21 of 26 (81%) control dogs. In that situation, owners reported a perceived clinical improvement in 17 dogs.

Concurrent disease was identified in 15 (48%) case dogs and 8 (15%) control dogs. Diseases included cardiac disease, hypothyroidism, clostridial enterotoxicosis, brachycephalic upper airway syndrome resulting from stenotic nares or elongation of the soft palate, and various urogenital diseases. The distribution of the various types of concurrent disease did not differ significantly (P = 0.63) between groups.

Causes of bromism—A suspected cause of bromism was recorded in the medical records of 29 case

dogs. Suboptimal monitoring of serum concentrations of bromide was the most commonly implicated reason for development of bromism and was reported for 14 of 29 (48%) case dogs. For 6 dogs, a multifactorial cause of bromism was suspected: suboptimal treatment monitoring combined with a reduction in renal function (4 dogs with chronic renal failure and 1 dog with pyelonephritis) and suboptimal treatment monitoring and iatrogenic bromide dosing error (1 dog). For 2 dogs with chronic renal failure, bromism was attributed to the reduction in renal function.

Iatrogenic bromide dosing errors were identified in the records of 4 case dogs. In 2 case dogs, the prescribed formulation was changed from the potassium salt to the sodium salt of bromide to reduce vomiting associated with bromide administration; however, the bromide dose was not reduced. In the other 2 dogs, the concentration of administered bromide was increased (ie, from 250 mg/mL to 500 mg/mL) without a recommended concurrent volume reduction. This happened when various pharmacies were contracted to compound the bromide. Exposure to sources of bromide other than bromide compounded for anticonvulsant use was reported for 3 dogs. Two dogs had imbibed water from a bromide-tainted source (well water [bromide content, 3.1 mg/mL] or chemically treated spa water [bromide content, 8.3 mg/mL]). The third had been treated for a long period with an over-the-counter medicinal NSAID product that contained bromide (bromide content, 40 mg/mL). That dog had received 21 mg/kg/d (9.5 mg/lb/d) of bromide more than the dosage typically prescribed for anticonvulsant use.

Associations of variables with bromism—Univariate analyses revealed that none of the categoric variables were significantly ($P \leq 0.1$) associated with bromism. These variables included dog sex, bromide formulation, bromide dosing interval, total number of prescribed bromide dose changes in the year preceding referral to the veterinary hospital, concurrent treatment with phenobarbital, phenobarbital dosing interval, concurrent medications, or concurrent disease. On the other hand, several continuous variables were significantly ($P \leq 0.1$) associated with the development of bromism according to the requirements for consideration for the multivariate model (**Table 1**). With the exception of dietary chloride content, no dietary factor (diet type, manufacturer, brand, amount, dietary sodium content, and frequency of feeding) was significantly ($P \leq 0.1$) associated with the development of bromism.

The final multivariate modeling process identified total daily bromide dose at admission and serum concentrations of urea nitrogen and sodium as associated with development of bromism, although only total bromide dose at admission was significant ($P < 0.05$; **Table 2**). For a 5 mg/kg (2.27 mg/lb) increase in the total daily dose of bromide, the odds of having bromism increased almost 5-fold. Among these variables, all 2-way interactions were tested one at a time, and none were significant.

Table 1—Results of univariate analyses of continuous variables evaluated for an association with bromism in dogs with idiopathic epilepsy.

	Dogs with bromism		Dogs without bromism		
Variable	**No.**	**Mean ± SEM**	**No.**	**Mean ± SEM**	***P* value***
Age (y)	31	7.2 ± 0.5	52	6.2 ± 0.4	0.08
Body weight (kg)†	31	24.9 ± 3.1	52	22.5 ± 3.1	0.53
Body condition score‡	31	5.9 ± 0.3	52	6.0 ± 0.2	0.80
Duration of epilepsy (y)	27	4.5 ± 0.5	46	4.3 ± 0.4	0.67
Duration of phenobarbital treatment prior to admission (d)	24	1,499 ± 160	40	1,144 ± 124	0.08
Serum phenobarbital concentration at admission (µg/mL)	26	31.4 ± 1.2	41	26.7 ± 1.0	0.003
Total daily phenobarbital dose at admission (mg/kg)†	26	6.3 ± 0.4	43	6.5 ± 0.3	0.68
Total daily bromide dose at admission (mg/kg)†	31	44.9 ± 1.7	52	28.4 ± 1.3	< 0.001
Serum bromide concentration at admission (mg/mL)	31	3.7 ± 0.3	52	1.7 ± 0.1	< 0.001
Serum bromide concentration monitoring interval (d)	28	556 ± 54	47	221 ± 42	< 0.001
Last serum bromide concentration prior to referral (mg/mL)	21	1.9 ± 0.3	44	1.7 ± 0.2	0.13
Duration of bromide treatment prior to admission (d)	31	1,101 ± 158	50	975 ± 128	0.51
Hct (%)	29	39 ± 4.5	49	35 ± 5.1	0.17
SUN (mg/dL)	31	32 ± 3.0	52	23 ± 2.3	0.01
Serum creatinine (mg/dL)	31	1.8 ± 0.4	52	1.2 ± 0.3	0.003
Serum sodium (mEq/L)	31	146 ± 2.3	52	143 ± 1.8	< 0.001
Serum chloride (mEq/L)	31	145 ± 13	52	121 ± 9	< 0.001
Serum potassium (mEq/L)	31	3.6 ± 0.2	52	3.4 ± 0.4	0.59
Serum alanine aminotransferase (U/L)	31	159 ± 25	52	147 ± 41	0.66
Serum alkaline phosphatase (U/L)	31	217 ± 36	52	283 ± 27	0.19
Serum bilirubin (mg/dL)	31	0.3 ± 0.1	52	0.2 ± 0.1	0.58
Serum cholesterol (mg/dL)	31	291 ± 62	52	284 ± 48	0.84
Serum glucose (mg/dL)	31	121 ± 18	52	134 ± 23	0.57
Serum globulin (g/dL)	31	3.8 ± 0.7	52	4.1 ± 1.0	0.66
Serum albumin (g/dL)	31	3.4 ± 0.4	52	3.2 ± 0.6	0.61
Dietary chloride (% dry matter)	30	0.51 ± 0.01	50	0.48 ± 0.01	0.003

*A value of $P \leq 0.10$ was considered significant for the purpose of considering the associated variable for inclusion in a multivariate model.
†To convert kilograms to pounds, multiply by 2.2. ‡Body condition was assessed by use of a 9-point scale.

Table 2—Results of final multivariate conditional logistic regression model of variables potentially associated with development of bromism in dogs (31 dogs with bromism and 52 dogs without bromism).

Risk factor	Odds ratio*	95% confidence interval	*P* value†
Total daily bromide dose at admission	4.7	1.2–18.1	0.02
SUN concentration	1.2	0.9–1.6	0.15
Serum sodium concentration	3.7	0.3–42.4	0.30

*All odds ratios are based on an increase of 5 respective and specific units for each risk factor (5 mg/kg for bromide dose, 5 mg/dL for SUN concentration, and 5 mEq/L for serum sodium concentration). †A value of $P < 0.05$ was considered significant.

Discussion

Results of the study reported here supported other findings that suggest bromism is an intoxication that can manifest as heterogeneous clinical signs of peripheral and CNS dysfunction. Similar neurologic signs have been detected in other dogs with naturally developing and experimentally induced bromism.[2,5,7–9] Results of the present study also suggested that observable or inducible signs and historic evidence of pain are notably lacking in dogs with neurologic signs of spinal cord lesions that resulted from bromism. Veterinarians should therefore consider bromism as a possible differential diagnosis in dogs with idiopathic epilepsy that are treated with bromide and have neurologic signs, and they should recognize that neurogenic weakness caused by bromism can selectively affect the limbs and result in signs of UMN and LMN abnormalities, similar to findings in humans.[10] The mechanisms by which bromide exerts an anticonvulsant activity or causes neurotoxic effects are currently unknown, but in humans, a reduction in cerebral blood flow that is reversible after diuresis or dialysis is believed to play a role.[14]

Evidence from experimental studies[3–7] indicates that bromism develops in a dose-dependent fashion in healthy dogs, and other investigators have suggested that the neurologic manifestations of bromism may develop in a similar manner in bromide-treated dogs with idiopathic epilepsy. The results of the present study indicated that the total daily dose of bromide was a significant risk factor for bromism, and for each 5 mg/kg increase in this dose, the odds of having bromism increased considerably. The mean total daily bromide dose and mean serum bromide concentration in the present study exceeded the upper reference limits of bromide dose and therapeutic reference ranges commonly recommended when dogs are treated with the potassium salt of bromide and concurrent phenobarbital therapies.[1–4] Clinical experience and results of other studies[4–6] indicate that most dogs with idiopathic epilepsy, a steady-state serum concentration of phenobarbital within the approximate range of 10 to 40 µg/mL, and treatment with adjunctive bromide can achieve adequate seizure control with a steady-state serum concentration of bromide within the range of 1 to 2.5 mg/mL. Dogs treated with bromide alone may require a higher (2 to 3.5 mg/mL) serum bromide concentration.[4–6] Results of the study reported here suggest that veterinarians managing dogs with idiopathic epilepsy should be cognizant of the risk for the development of bromism when approaching the recommended upper limit of the bromide dose range.

Several other results of the present study, although not significant, may be clinically important. Suboptimal frequency of monitoring of serum bromide concentrations was identified as the most common cause of bromism in the present study. Findings from our study and others[4,11] suggest that monitoring of serum bromide concentration is important for identifying pharmacokinetic trends in individual dogs with idiopathic epilepsy and for avoiding or confirming toxicosis and treatment failure. The bromide monitoring interval was twice as high in dogs with bromism (556 days), compared with the interval in dogs without bromism (221 days). It is important to mention that both of these intervals exceeded the recommended maximum interval of 180 days for dogs with steady-state serum bromide concentrations.[3]

Some dogs with bromism had not been assessed for serum bromide concentration before they were referred to the teaching hospital, despite having received long-term treatment with bromide. In addition, the serum bromide concentration in dogs with bromism nearly doubled during the monitoring interval that preceded the diagnosis of bromism, whereas the serum bromide concentration remained stable in dogs without bromism.

Several factors likely contribute to within-dog fluctuations in bromide concentrations that cannot be readily predicted or identified without treatment monitoring. Therefore, regular measurements of serum concentrations of anticonvulsant drugs as well as comprehensive clinicopathologic assessments (CBC, serum biochemical analysis, and urinalysis) should be incorporated into routine monitoring regimens for dogs with idiopathic epilepsy. In our hospital, we routinely perform these tests in epileptic dogs at least every 6 months once a steady state in serum anticonvulsant concentration has been achieved, although other authors may recommend a different interval.[1,3,5,6,11] These tests serve to screen for concurrent disease conditions (eg, decrease in glomerular filtration rate) or a change in serum bromide concentration that might predict future development of a drug-related toxicosis.[2,3] Reliance on historic or clinical markers of coexistent renal disease in dogs with idiopathic epilepsy treated with bromide or a combination of anticonvulsant drugs may be challenging because classic clinical signs of renal disease (ie, polyuria or polydipsia) are identical to the adverse effects commonly associated with anticonvulsant drug administration and which owners of dogs with idiopathic epilepsy may come to accept as a consequence of treatment.

The results reported here also highlight other potential etiologies of bromism, which to the authors' knowledge, have not been reported in the veterinary literature. Three dogs developed bromism after consumption of nonprescription sources of bromide, such as bromide-tainted well water and whirlpool spa water, and long-term administration of an imported, over-the-counter medicinal bromide product. These possible exogenous sources of bromide have been implicated in human cases of bromism.[10,15,16] The results of the present study also suggested that when various pharmacies are contracted to compound bromide for individual dogs, prescribing veterinarians should ensure that bromide formulations remain consistent to prevent inadvertent bromide dosing errors.

Most dogs with bromism in the study reported here had a rapid clinical improvement with treatment, required only short periods of hospitalization, and ultimately had a satisfactory clinical recovery despite a wide range in severity and clinical manifestations of bromism. This finding was likely attributable to the fact that 87% of dogs were treated aggressively with measures intended to facilitate renal excretion of bromide in combination with a reduction in bromide dose. Dogs that received such treatment had a more rapid recovery from bromism than those that had only a reduction in bromide dose. The potential was also detected for breakthrough seizures as a complication of a reduction in serum bromide concentration during diuresis or following bromide dose reduction, as was evident in 26% of dogs. Owners of dogs with bromism should be advised of the potential for breakthrough seizures because such a loss of seizure control can result in an increase in duration of hospitalization and long-term expenditures should emergency anticonvulsant treatment or additional maintenance anticonvulsant drugs be required or recommended. It has been reported that delivery of IV administered physiologic saline solution at a maintenance rate for < 24 hours is typically sufficient to resolve clinical signs of bromism.[6]

Although all dogs with bromism in the present study improved clinically, signs of bromism did not resolve in all dogs following a reduction in the serum bromide concentration. This may be explained by variability in tolerances of individual dogs to bromide, the additive or synergistic effects of concurrent phenobarbital treatment, the existence of undiagnosed concurrent neurologic disorders, or existence of permanent bromide-induced neuronal atrophy or dysregulation of neurotransmission.[17]

The failure of this study to reveal risk factors for bromism other than bromide dose was likely attributable to the small size of the case population and the inherent limitations of retrospective studies in regard to completeness and uniformity of information available in medical records. The codependence of several of the variables identified during the multivariate modeling procedure likely contributed to the lack of significant findings as well.

Results of the present study suggested that bromism in dogs is a dose-dependent neurotoxicosis that can cause varied clinical signs attributable to multiple neuroanatomic locations. Clinical manifestations of bromism are rapidly and largely reversible with diuresis and bromide dose reduction. When treating dogs with bromism, IV administration of physiologic saline solution for induction of diuresis should be performed judiciously and in conjunction with serial monitoring of serum bromide concentrations to avoid breakthrough seizures. When managing dogs with idiopathic epilepsy treated with bromide, regular monitoring of serum bromide concentrations is recommended to identify factors that potentially influence the pharmacokinetics of bromide and optimize the effects of anticonvulsant treatment in individual dogs.

a. Automated measurement via Roche/Hitachi 912, Roche Diagnostics Division, F. Hoffmann-La Roche Ltd, Basel, Switzerland.
b. Direct gold-trichloride measurement via VetSpec bromide kit, Catachem Inc, Bridgeport, Conn.
c. Gas chromatographic-mass spectroscopic measurement via Agilent 6890 N Network GC System/5973 MS Detector, Agilent Technologies Inc, Santa Clara, Calif.
d. Olympus AU400, Olympus America Inc, Melville, NY.
e. SAS, version 9.1.3, SAS Institute Inc, Cary, NC.

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