Disposition and clinical use of bromide in cats

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Objective—To establish a dosing regimen for potassium bromide and evaluate use of bromide to treat spontaneous seizures in cats.

Design—Prospective and retrospective studies.

Animals—7 healthy adult male cats and records of 17 cats with seizures.

Procedure—Seven healthy cats were administered potassium bromide (15 mg/kg [6.8 mg/lb], PO, q 12 h) until steady-state concentrations were reached. Serum samples for pharmacokinetic analysis were obtained weekly until bromide concentrations were not detectable. Clinical data were obtained from records of 17 treated cats.

Results—In the prospective study, maximum serum bromide concentration was 1.1 ± 0.2 mg/mL at 8 weeks. Mean disappearance half-life was 1.6 ± 0.2 weeks. Steady state was achieved at a mean of 5.3 ± 1.1 weeks. No adverse effects were detected and bromide was well tolerated. In the retrospective study, administration of bromide (n = 4) or bromide and phenobarbital (3) was associated with eradication of seizures in 7 of 15 cats (serum bromide concentration range, 1.0 to 1.6 mg/mL); however, bromide administration was associated with adverse effects in 8 of 16 cats. Coughing developed in 6 of these cats, leading to euthanasia in 1 cat and discontinuation of bromide administration in 2 cats.

Conclusions and Clinical Relevance—Therapeutic concentrations of bromide are attained within 2 weeks in cats that receive 30 mg/kg/d (13.6 mg/lb/d) orally. Although somewhat effective in seizure control, the incidence of adverse effects may not warrant routine use of bromide for control of seizures in cats. (*J Am Vet Med Assoc* 2002;221:1131–1135)

Whereas epilepsy affects up to 3% of the canine population, the percentage of the feline population affected by epilepsy is unknown, although this disease appears to be less common than in dogs.[1] This may reflect, in part, the likelihood that seizure disorders in cats are more likely to be caused by structural brain diseases rather than being the result of idiopathic or hereditary epilepsy.[2] It is not surprising, therefore, that the number of drugs recommended to treat epilepsy in cats is limited. Presently, the most commonly recommended first- and second-choice anticonvulsants for treatment of seizures in cats are, respectively, phenobarbital and diazepam.[3-5] Both drugs are cleared by hepatic metabolism, a process in which cats are generally recognized to be deficient.[6] Phenobarbital has an elimination half-life of 59 hours in cats.[7,8] Although phenobarbital has proven efficacious for seizure control in cats[9] and generally is considered safe, its use can be associated with adverse effects, including sedation (which may be more pronounced than in dogs), polyuria, polydipsia, and cerebellar signs.[10] In 1 report of treated cats, 10% developed clinical signs consistent with drug allergy (thrombocytopenia, transient facial pruritis, and neutropenia).[9] Additionally, phenobarbital administration has been associated with coagulopathy in cats.[11] Although apparently not documented in cats, phenobarbital is likely to cause hepatotoxicosis in cats, as in dogs. Additionally, although not documented in cats, phenobarbital is a potent inducer of hepatic drug-metabolizing enzymes in several species including dogs.[12-15] Enzyme induction can cause decreased drug elimination half-life for phenobarbital, other drugs, and endogenous compounds such as thyroid hormones,[16] and cause changes in hepatic enzymes that might be clinically confused with hepatic disease. Finally, our experience with therapeutic drug monitoring of phenobarbital in cats suggests that small incremental changes in doses may at times result in markedly greater than anticipated changes in drug concentrations, leading either to treatment failure or unacceptable sedation. Primidone, a drug historically used to treat seizures in dogs because of its conversion to phenobarbital, is not recommended in cats, in part, because of toxicity at therapeutic doses[17] and poor conversion to phenobarbital.[18] Because feline epilepsy does not appear to become refractory to treatment with diazepam as does canine epilepsy,[19] diazepam often is cited as a second drug of choice for treatment of feline epilepsy. Characterized by an elimination half-life of 15 to 20 hours in cats,[1] diazepam does appear to be clinically effective. However, up to 20% of cats reportedly are unresponsive to diazepam treatment.[1] Additionally, diazepam causes sedation and weight gain that may be unacceptable to pet owners.[1] Even more problematic are reports associating diazepam, when used as an appetite stimulant, with irreversible hepatotoxicosis in cats.[20-22] Thus, there is a need for a safe, effective alternative antiepileptic in cats.

Bromide is the natural state of the bromine ion. Although bromide was the first anticonvulsant used to treat seizures in humans,[23,24] its use was discontinued in the early 1900s with the introduction of phenobarbital. As such, the compound is not an approved drug and must be purchased (eg, by practitioners or pharmacists) as medicinal grade (as either the potassium or sodium salt) from chemical companies. The mechanisms of anticonvulsant and sedative effects of bromide are not known. Interaction between bromide and neuronal membranes leading to increased chloride flux, or inhibition of carbonic anhydrase or bicarbonate ATPase have been postulated.[25,26] More recent evidence

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indicates that bromide prolongs inhibitory postsynaptic currents in the cerebral cortex by 30 to 50%, thus enhancing inhibition.[a] Regardless of its mechanism, bromide has been used since the early 1990s[27-30] as an adjunctive anticonvulsant for canine patients unresponsive to phenobarbital and is increasingly selected as a first-choice sole anticonvulsant in dogs. The characteristics of bromide that favor its use as an anticonvulsant include renal elimination,[31] which minimizes the risk of hepatic and drug interactions; efficacy that appears to be related to plasma drug concentrations; reasonable cost and availability; the availability of therapeutic drug monitoring to guide dosing regimens[32]; and long elimination half-life (25[33] to 46[34] days in dogs). This latter characteristic provides a measure of protection not provided by many other anticonvulsants by rendering negligible the fluctuations of plasma drug concentrations during a 12- or 24-hour dosing interval. Reported drug interactions in veterinary medicine (other than a combined sedative effect when used with phenobarbital) are limited to a diet-drug interaction between bromide and sodium chloride content in the diet. Renal bromide clearance decreases in the presence of high dietary chloride. Elimination half-life ranges from 8 to 38[35] days in the presence of a low-salt and nonrestricted salt diet, respectively.[36,37] Adverse effects of bromide reported in dogs most commonly are neurologic (sedation, ataxia) or gastrointestinal (vomiting, anorexia, or diarrhea, probably because of the hypertonic and osmotic nature of the salt) and are often concentration dependent.[38,39]

As a renally eliminated drug, the magnitude of differences in drug disposition in cats, compared with dogs, is expected to be less than for drugs that are metabolized by the liver.[5,6] Thus, on the basis of anticipated differences in drug disposition, bromide should be a reasonable alternative anticonvulsant for treatment of epileptic cats. However, use should be based on scientific studies that determine a dosing regimen, as well as clinical efficacy and safety in animals with spontaneous seizure disorders. The purpose of this study was to determine a dosing regimen for bromide in cats that would attain therapeutic serum concentrations of bromide that have been recommended in dogs and evaluate effectiveness and safety of bromide when used to control spontaneous seizures in cats.

Materials and Methods

Experimental studies—Bromide disposition was studied in 7 apparently healthy male neutered cats 1.5 to 2 years old that weighed approximately 6 kg (13.2 lb). The cats were housed in individual cages at the Veterinary Teaching Hospital Small Animal Clinic. Cats were acclimated to the environment and fed a standard hospital diet[b] throughout the study that was offered in 2 divided meals just prior to drug dosing during the study. All experimental protocols were approved by the University Laboratory Animal Care Committee, which ensures compliance with the National Institute of Health's *Guide for the Care and Use of Laboratory Animals* and the Animal Welfare Act. The health of each cat was assessed by use of physical examination and a minimum database that comprised results of CBC, serum biochemical analyses (serum alanine transaminase, aspartate transaminase, and alkaline phosphatase activities; and serum urea nitrogen, creatinine, albumin, total protein, calcium, glucose, cholesterol, sodium and potassium concentrations), and a routine urinalysis. Each cat was weighed prior to the start of the study and each week of the study on the day of trough sample collection. Daily doses of potassium bromide were calculated for each cat to the nearest 5 mg by use of the recommended canine dose of 15 mg/kg (6.8 mg/lb) administered every 12 hours orally prior to a morning and evening meal. Potassium bromide was formulated into gelatin capsules (size 3)[c] using lactose[d] as filler. Prior to the start of the study and once weekly, 5 mL of blood was collected prior to the morning dose for bromide analysis. Serum was harvested from samples within 2 hours of collection, and bromide was quantitated in the serum within 24 hours. Potassium bromide administration was continued daily until steady-state concentrations had been achieved. Steady-state concentrations were defined by serum drug concentrations that did not fluctuate > 10% (our acceptable amount of variability in the bromide assay) on 2 subsequent weeks in the same cat. Once steady state was achieved, potassium bromide dosing was discontinued in that cat. Weekly blood collection continued (at the same time samples were collected during dosing) in each cat until serum bromide concentrations were below the level of quantification for our laboratory. Safety of the drug was assessed by repeating the minimum database after the last dose of bromide, daily physical examinations, and comparison of body weights at the beginning and end of the study. The appetite of each cat was also assessed daily.

Serum bromide concentrations were quantitated within 24 hours of collection by use of ultraviolet spectrophotometry (wavelength, 440 nm) with the gold chloride method of detection.[40] The assay was validated by use of feline serum. Coefficients of variation for controls were 6.3% for 0.25 mg/mL (set as the lower limit of quantitation), 9.1% for 0.70 mg/mL, 7.4% for 1.60 mg/mL , and 9.1% for 3.75 mg/mL. Serum bromide concentration versus time was plotted semilogarithmically for each cat, and data were subjected to noncompartmental analysis[e] by use of the linear-log trapezoidal option for determination of the area under the concentration versus time curve. The dosing interval of 12 hours was much shorter than the half-life of the drug, and cats were dosed until steady state was reached. Thus, the data were modeled as a constant infusion into plasma with dosing information input as 15 mg/kg every 0.07 week for 8 weeks. Clinically relevant parameters that were determined from this data were limited to **maximum concentration (C_{max})** occurring at **time to maximum concentration (t_{max})**; for steady-state data, this time point corresponds to a data point collected during a dosing interval, **the rate constant of disappearance (k_d)**, and **disappearance half-life ($t_{1/2}$)**. The terminal component upon which the k_d was determined by use of log-linear regression was based in each cat on data collected on the last week of bromide administration (the first time point) and the lowest quantifiable concentration (the last time point). The k_d was then used to calculate the $t_{1/2}$ using the equation

$$t_{1/2} = 0.693/k_d$$ [41]

Because bromide was not administered IV and **bioavailibility (F)** is not known for bromide in cats, the **volume of distribution at steady state (Vdss)** and **clearance (CL)** could not be directly calculated. Hence, CL/F and Vdss/F are reported.[42] Likewise, the terminal component of the serum drug concentration versus time curve cannot be confirmed to represent elimination, and as such it and half-life calculated from its rate constant are referred to as disappearance rather than elimination. Time to steady state for each cat was defined as the time (week) at which serum bromide concentrations achieved at least 87.5% (3 $t_{1/2}$) of C_{max}. Pharmacokinetic data

are reported as mean ± SD with the exception of $t_{1/2}$, which is reported as harmonic mean and its comparable measure of SD, pseudostandard deviation. Clinical laboratory data and body weight determined at the beginning and end of the study were compared by use of a paired Student *t* test.

Retrospective studies—Medical records of feline samples submitted for serum bromide analysis to the therapeutic drug monitoring service at the Clinical Pharmacology Laboratory of the Texas Veterinary Medical Center were identified. Samples had been submitted by referring veterinarians after collection from cats with spontaneous diseases associated with seizures that received bromide as an anticonvulsant. Serum bromide analysis had been performed in the laboratory according to the methods described for the experimental study. Data submitted with the sample included signalment, dosing regimen (route, dose, and interval), duration of administration at the present dose, and present seizure status. Veterinarians who submitted the samples were contacted by telephone to collect additional information regarding evidence of adverse drug reactions at the time of sample submission with specific reference to vomiting, diarrhea, signs of sedation (ataxia, grogginess), coughing, and respiratory distress at any time during the administration of the drug. Descriptive statistics were generated for continuous and categoric data and reported as median and range.

Results

Bromide disposition in healthy male cats—Mean C_{max} of 1.1 ± 0.2 mg/mL (**Fig 1**) occurred at 8 weeks for all cats. Steady-state concentrations, defined as 87% of the C_{max}, occurred at a mean of 5.3 ± 1.1 weeks (Fig 1). Mean k_d was 0.45 ± 0.06/wk, resulting in mean $t_{1/2}$ of 1.6 ± 0.2 weeks. Mean accumulation ratio was 27 ± 10 and mean Vss/F and Cl/F were 0.44 ± 0.09 L/kg and 0.21 ± 0.03 L/kg/wk, respectively. All cats tolerated bromide administration well with no evidence of adverse effects including loss of appetite. Clinical laboratory data were within reference limits at all times, and neither these data nor body weight differed after the study, compared with corresponding values determined before the study.

Bromide use in cats with spontaneous seizures—Of 3,000 records reviewed for January 1998 to June 2001, records for 20 feline samples submitted for serum bromide analysis were examined. Of these 20 cats, records of 2 were submitted with insufficient information and the cats were lost to follow-up, and 1 record was from a lion, leaving 17 cats for inclusion. Not all data were available for all cats. Six cats were female, and 11 were male; all were neutered. All received bromide as the potassium salt. Thirteen cats were described as domestic short hair, 1 as domestic medium hair, 2 as domestic long hair, and 1 as Siamese. Mean ± SD values for selected variables included age at time of sample submission, 8.6 ± 3.9 years (n = 17); serum bromide concentration, 1.5 ± 0.7 mg/mL (17); bromide dose, 24.2 ± 11.23 mg/kg/d (11 ± 5.1 mg/lb/d; 16); and duration of treatment at the present dose, 12.5 ± 9.7 months (16). The daily dose was divided and administered at 12-hour intervals for 11 of 16 cats. Twelve of these 16 cats simultaneously received phenobarbital, with serum concentrations ranging from 13 to 47 µg/mL (n = 5). Seizure status was provided for 15 of the cats. For 7 of 15 cats, seizures were considered to be controlled (eradicated) at the time the sample was collected. Serum bromide concentrations ranged from 1.0 to 1.6 mg/mL in these cats; however, 3 of the 7 were also receiving phenobarbital. Serum bromide concentration in those cats not receiving phenobarbital was approximately 1.0 mg/mL. Eight cats continued to have seizures despite serum bromide concentrations that ranged from 0.4 to 1.7 mg/mL (5 of these 8 cats were also receiving phenobarbital). Four of the cats with seizures were euthanatized shortly after the bromide sample was collected because seizures were not sufficiently well controlled; 1 of these 4 cats was being treated for status epilepticus that had not responded to other anticonvulsant drugs. Bromide administration was associated with 1 or more adverse effects in 8 of 17 cats. Adverse effects included polydipsia, vomiting, or weight gain each in 1 cat, grogginess in 2 cats, and coughing in 6 cats. Coughing did not appear to be associated with drug concentration (serum bromide concentration range for coughing cats was 1.0 to 3.2 mg/mL) or duration of treatment (range of onset, 3 to 23 months). Coughing was often sudden in onset and associated radiographically with a severe bronchial pattern in 1 cat, which led to euthanasia. Coughing responded to a short course of glucocorticoid administration in 1 cat that continued to receive bromide. Coughing was sufficiently severe to cause discontinuation of bromide administration in 2 cats. Coughing declined during a 1-month period in both cats after bromide treatment was withdrawn. Two cats continued to receive bromide despite coughing; coughing improved in 1 of the cats, but had been present for 2 weeks in the second cat at the time this study was conducted.

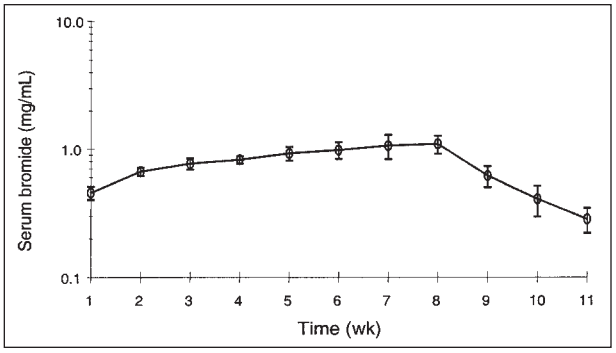

Figure 1—Mean ± SD log serum bromide concentration versus time curve in 7 healthy cats that were administered potassium bromide (15 mg/kg [6.8 mg/lb], PO, q 12 h) for 8 weeks.

Discussion

Previous reports of the use of bromide in cats have been limited to an abstract of the experimental portion of this report[f] and an abstract delineating adverse effects on the respiratory system associated with clinical use of bromide in cats.[g] Although the initial role of bromide treatment in small animals was as an adjuvant to phenobarbital administration in dogs with seizures that were unresponsive to phenobarbital, bromide is increasingly being used as the first drug of choice for treatment of seizures in dogs.[30-33] The fact that it is renally eliminated is particularly appealing for treatment in cats because of their unique deficiencies in hepatic drug metabolism.

Because bromide is renally eliminated, disposition of bromide in cats was not expected to markedly differ from that in dogs. Disposition of bromide in dogs has been reported only after administration of a single dose (20 mg/kg [9.1 mg/lb]); C_{max} after oral administration was 0.08 ± 0.013 mg/mL . Steady-state concentration in cats following administration at 30 mg/kg/d (13.6 mg/lb/d) was 1.09 ± 0.18 mg/mL. The difference in study design (single dosing compared with multiple dosing at steady state) between the 2 reports precludes direct comparisons of C_{max}. However, in our therapeutic drug monitoring service, mean concentration in dogs (n = 70) that received bromide at 30 mg/kg/d for ≥ 6 months was 1.4 ± 0.6 mg/mL. Bromide $t_{1/2}$ in cats is approximately one third (mean, 1.56 ± 0.21 weeks) of that reported in dogs (5.3 ± 1.4 weeks).[h] Half-life is influenced by Vdss and CL. Comparisons of these 2 parameters for bromide in dogs and cats is complicated by lack of IV administration in our study. Both Vdss and CL would be increased equally by the fraction of drug that does not reach systemic circulation (ie, not absorbed) following oral administration (ie, F). Thus, comparisons between dogs and cats for these 2 parameters must be adjusted for differences in F (ie, Vdss/F and CL/F). Dogs receiving a single dose of bromide were reported to have Vdss of 0.45 ± 0.7 L/kg (0.2 ± 0.3 L/lb) and CL of 0.063 ± 0.027 L/kg/wk (0.03 ± 0.01 L/lb/wk). Cats had Vdss/F of 0.44 ± 0.09 L/kg (0.2 ± 0.04 L/lb) and CL/F of 0.21 ± 0.03 L/kg/wk (0.1 ± 0.01 L/lb/wk) for bromide. Comparison suggests that the Vdss of bromide in cats and dogs may be similar, but CL of bromide may be greater in cats. Differences in CL could explain the apparent differences in disappearance half-life of bromide between dogs and cats.

Based on the measured $t_{1/2}$ of 1.6 weeks, the predicted time to steady state should have been 4.8 to 8 weeks (3 to 5 drug half-lives). This was supported by a calculated time to steady state of 7.6 weeks, although concentrations had essentially reached the minimum therapeutic concentration recommended by our laboratory (for dogs) by 3 weeks in all cats. This study revealed that $t_{1/2}$ of bromide is shorter in cats, compared with dogs, and that steady state may develop more rapidly in cats. The need for loading doses intended to rapidly achieve therapeutic concentrations is not as obvious in cats. We choose not to dose cats with a loading dose of bromide because of concern for gastrointestinal irritation.

The experimental portion of our study must be interpreted in the context of the retrospective clinical portion of the study. First, therapeutic concentrations have not been established for bromide in cats. Our results suggest that seizures in cats may not respond to bromide as well as in dogs. Seizures were considered controlled (eradicated) in only 6 of 17 cats, despite bromide concentrations of 1.0 to 1.6 mg/mL, and almost half of these cats were also receiving phenobarbital; in comparison, 72% of seizures in dogs are controlled with bromide. Uncontrolled seizures led to euthanasia in 4 cats. Thus, results suggest that the therapeutic range for bromide may differ between cats and dogs and that cats do not respond as well.

Second, whereas results of the experimental portion of this study suggested that potassium bromide could be used safely in cats for 8 weeks with minimal adverse effects, the results of retrospective clinical portion of this study suggested otherwise. Bromide use was associated with a reported adverse effect in 8 of 17 cats studied retrospectively. Disconcertingly, coughing developed in 6 of 17 cats, with onset between 2 weeks and 23 months after initiation of treatment with bromide. More importantly, coughing led to euthanasia in 1 cat; total mortality rate was 5 of 17 cats studied retrospectively. In a previous report[h] of cats that received bromide, a similar incidence (42%) of coughing was noted. In that study, clinical signs appeared at 7 weeks to 14 months and 2 of 26 cats died as a result of airway disease. The association of coughing with bromide was supported in our study by the complete resolution of coughing that occurred in 1 cat within 1 month of discontinuing treatment; coughing did not return during the next year. Wagner[h] reported a similar resolution of signs after bromide administration was discontinued, although an interval of 16 months was necessary between discontinuation of treatment and resolution of coughing in 1 cat. Results of that study suggest that bromide may not be a safe drug to use in cats, particularly compared with its use in dogs, because of the risk of clinical signs consistent with bronchial asthma, which may be life threatening. Thus, bromide should be used cautiously in cats with seizures until additional information regarding safety and efficacy is available. Based on the author's experience, if a cat receiving bromide subsequently develops adverse respiratory effects, use of glucocorticoids may alleviate clinical signs consistent with asthma, although Wagner[h] noted that neither antibiotics nor corticosteroids were beneficial unless bromide administration was discontinued.

A cause and effect relationship between bromide and clinical signs consistent with bronchial asthma is not obvious. Because of its influence on chloride movement in the body, bromide administration might affect bronchial secretions and thus alter mucociliary function, although evidence could not be found in the literature to support such an effect. However, evidence does exist for a relationship between bromide and eosinophils. The lack of association between concentration (dose) or duration of bromide administration and coughing in cats supports an allergic rather than dose-dependent relationship. Allergic responses to bromide have been reported in the human literature. Bromide has long been recognized to cause pruritis; indeed, the term bromoderma is used to refer to a bromide-associated skin lesion in humans. Tissue damage associated with eosinophil influx has been postulated to reflect bromination of a tyrosine residue, resulting in an increase in peroxidase in eosinophils.[43] An increase in brominated oxidation products has been associated with asthmatic, but not clinically normal, humans. Stimulation of cytokines by bromide also has been postulated.[44] In our study, clinical laboratory data, including eosinophil counts, were not available from coughing cats that received bromide. However, Wagner[h] detected severe eosinophilic infiltration via bronchoalveolar lavage in 2 cats that received bromide and

a mixed neutrophilic-eosinophilic cell population in a third.[h] Further exploration of the cause and effect relationship between bromide, eosinophilia, and coughing in cats is indicated.

[a]Gutnick M, Koret School of Veterinary Medicine, Jerusalem: Personal communication, 2001.
[b]Science Diet Feline Maintenance, Hill's Pet Food, Topeka, Kan.
[c]Frontier, Norway, Iowa.
[d]Lactose, Fisher Scientific, Pittsburgh, Pa.
[e]WinNonlin, Pharsight, Cary, NC.
[f]Boothe DM, Kelly G. The disposition of bromide in cats following oral administration of the potassium salt (abstr), in *Proceedings*. 14th Am Coll Vet Intern Med Forum 1996;105:757.
[g]Dewey C, Ducote J, Coates J, et al. Intrarectally administered potassium bromide loading in normal dogs (abstr), in *Proceedings*. 17th Am Coll Vet Intern Med Forum 1999;17:745.
[h]Wagner SO. Lower airway disease in cats on bromide therapy for seizures (abstr), in *Proceedings*. 19th Am Coll Vet Intern Med Forum 2001;19:562.

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