

Effects of Chloride in the Diet on Serum Bromide Concentrations in Dogs

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ABSTRACT

Potassium bromide (KBr) is an antiepileptic drug used widely for seizure control in dogs. Diets with high chloride content have been shown to decrease serum bromide concentrations in dogs. However, the relationship between dietary chloride intake and serum bromide concentrations currently remains unknown. The aim of the present study was to clarify the relationship between serum bromide concentration and dietary chloride intake in order to contribute to the treatment of epilepsy in dogs on bromide. Steady-state serum bromide concentrations were measured using a gold chloride method in 23 dogs treated with KBr. The content of chloride (per 1g) was measured using Mohr's method or calculated from the ingredients label provided by the manufacturer. A regression analysis was used to evaluate the

relationship between dietary chloride intake (mg/kg/day) and the serum bromide concentration per dose ($\mu\text{g/ml}$ per mg/kg). Dogs with a higher chloride intake had lower serum bromide concentrations. A strong negative correlation was observed between dietary chloride intake (mg/kg/day) and the serum bromide concentration per dose ($\mu\text{g/ml}$ per mg/kg) ($P < 0.01$). These results suggest the importance of considering the dietary content of chloride for KBr-treated dogs and may also assist with the selection of KBr doses and appropriate diets by clinicians for dogs treated with KBr.

INTRODUCTION

Bromide is an antiepileptic drug (AED) used widely for seizure control in dogs since the early 1990s.¹⁻⁴ It is commonly administered as potassium bromide (KBr) or, in some situation, as sodium bromide (NaBr). Bromide is reportedly effective both as a monotherapy⁵ and add-on treatment.^{3, 4, 6-9}

Today, bromide is widely used as a first and second line AED for dogs because of its efficacy, wide safety margin, and infrequency of dosing.

Bromide is excreted in the urine without being metabolized in the liver because the molecule is very small.¹⁰⁻¹³ This pharmacokinetic property makes bromide especially useful for seizure control in animals with hepatic dysfunction. Since the amount of bromide excreted depends on the total body halide concentration,¹⁴ bromide excretion is influenced by the systemic chloride concentration. Recently, it was reported that the serum bromide concentration decreases with higher sodium and chloride contents in infusion fluids in dogs.¹⁵ Also, in both an experimental study and a clinical setting, diets with high contents of chloride were shown to decrease serum bromide concentrations in dogs.^{16,17} Hence, animals on bromide should not be fed salty foods and chloride in the diet should be kept stable. However, there are various diets including commercial diets and prescription diets, with various content of chloride. Individual dietary chloride intake thus varies, and some dogs have high dietary chloride intake. For example, a high chloride content diet may be given to dogs with urolithiasis as part of their treatment. Urolithiasis is a common urinary tract disease that can occur in dogs with epilepsy and on a bromide. In such cases, considering the dietary chloride intake is critical because high chloride intake will decrease the serum bromide concentration and worsen seizure control.

The aim of the present study was to quantify serum bromide concentrations in dogs fed diets with different contents of chloride, to clarify the relationship between serum bromide concentration and dietary chloride intake, and thereby contribute to the treatment of epilepsy in dogs on bromide.

MATERIALS AND METHODS

Animals

Twenty-three client-owned dogs treated with KBr and meeting the inclusion criteria below (a or b) were enrolled in the study. The

inclusion criteria were:

- a. Serum bromide concentration at steady-state, or
- b. KBr administered at the same dose for at least 4 months.

Thirteen dogs presented to Azabu University Veterinary Teaching Hospital, while the remaining 10 dogs presented to Watanabe Animal Hospital. Informed consent for research participation was obtained from all owners.

Information Collection and Questionnaire for the Owner

The dose of KBr, body weight and cause of epilepsy were investigated from medical records. Owners were questioned about their dog's diet by questionnaire. The questionnaire included information about the type of diet, amount of diet (g/day), number of meals (/day), and any foods given beside the main diet.

Measurement of the Concentrations of Serum Bromide and Dietary Chloride

A gold chloride method was applied for the measurement of serum bromide.¹⁵ Dietary chloride was measured using the titration methods of Mohr^{18,19} or calculated from the ingredient label provided by the manufacturer.

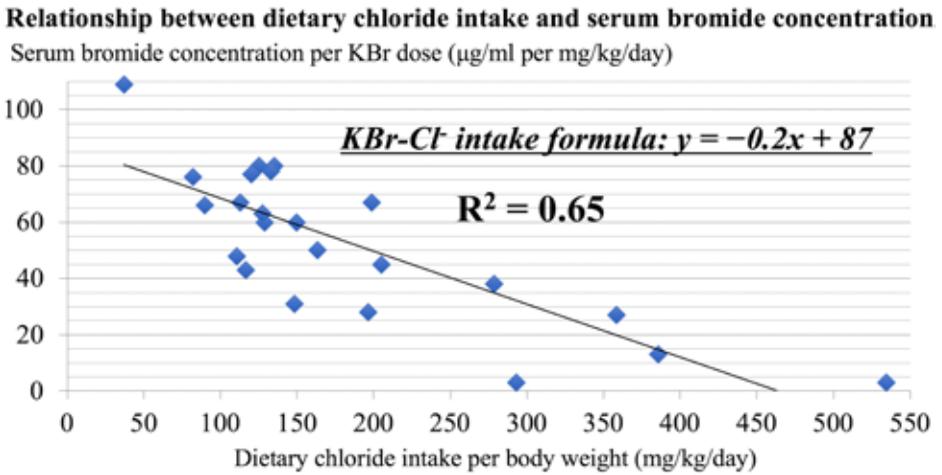
Data Analysis

To quantify the relationship between dietary chloride intake and serum bromide concentration, the two parameters below (a and b) were calculated and their numerical relationship was examined.

- a. Dietary chloride intake (mg/kg/day)
 - Dietary chloride intake (mg/kg/day) = Daily amount of diet (g/kg/day) × chloride content of the diet (mg/g)
 - Daily amount of diet (g/kg/day) = Amount of diet (g/time) × Times (/day) / Body weight (kg)
- b. Serum bromide concentration per KBr dose (µg/ml per mg/kg/day)
 - Serum bromide concentration (µg/ml) / KBr dose (mg/kg/day)

The formula describing the relation-

Figure 1. The relationship between dietary chloride intake (mg/kg/day) and serum bromide concentration per KBr dose (µg/ml per mg/kg/day). A strong negative correlation was observed between the parameters ($P < 0.01$). The numeric relationship of the two parameters is shown in the KBr-Cl- intake formula.



ship of the dietary chloride intake and serum bromide concentration was determined based on the parameters above. This formula was applied to two clinical cases and its usefulness was evaluated.

Clinical Application

Case 1 was receiving a prescription diet for the prevention of urolithiasis. The dog was on KBr with the standard recommended dose, but did not have good seizure control. The formula was applied for decision-making to gain better seizure control.

Case 2 was receiving a prescription diet for the prevention of kidney disease. The dog had a newly occurring seizure and was medicated with KBr but the seizure continued. The formula was applied at the time when the KBr dose was increased.

Statistical Analysis

Spearman's rank correlation coefficient was utilized to evaluate the relationship between the dietary chloride intake per body weight (mg/kg/day) and serum bromide concentration per KBr dose (µg/ml per mg/kg/day). The relationships between each parameter, i.e., dietary chloride intake per body weight (mg/kg/day), serum bromide concentration per KBr dose (µg/ml per mg/kg/day), daily amount of diet (g/kg), chloride content in the

diet (mg/g), and body weight (kg), were also examined using Spearman's rank correlation coefficient. A value of $P < 0.05$ was considered significant. Statistical analyses were performed using JMP®7.0.1 (SAS Institute).

RESULTS

Twenty-three client-owned dogs with a mean (\pm SD) body weight of 9.7 ± 8.8 kg (minimum to maximum, 0.74–40.2 kg) and a mean age of 8.0 ± 2.8 years (minimum to maximum, 3–12 years) were enrolled. There were 5 sexually intact females, 10 spayed females, 2 sexually intact males, and 6 castrated males. Breeds of dogs represented in the study included pug ($n = 4$), toy poodle ($n = 2$), Shetland sheepdog ($n = 2$), border collie ($n = 2$), beagle ($n = 2$), mixed-breed dog ($n = 2$), and one each of miniature dachshund, Yorkshire terrier, French bulldog, American cocker spaniel, miniature schnauzer, Pekingese, Boston terrier, Italian greyhound, and Great Pyrenees. Diagnoses of dogs represented in the study were idiopathic epilepsy ($n = 20$), meningoencephalitis of unknown origin ($n = 2$), and 1 hydrocephalus. All of the dogs' diets were dry type. All of the dogs had little or no treatment in feed beside the main diet. Nineteen dogs were measured for dietary chloride using Mohr's method, and

for the remaining 4 dogs the ingredients label provided by the manufacturer was used.

A significant strong negative correlation was observed between the dietary chloride intake (mg/kg/day) and serum bromide concentration per KBr dose ($\mu\text{g/ml}$ per mg/kg/day) ($r = 0.81$, $P < 0.01$) (Fig. 1). The numeric relationship of the two parameters was KBr-Cl- intake formula: $y = -0.2x + 87$ (x: dietary chloride intake, y: serum bromide concentration per KBr dose). A significant positive correlation was observed between serum bromide concentration per dose ($\mu\text{g/ml}$ per mg/kg/day) and body weight ($r = 0.65$, $P < 0.01$). A significant negative correlation was observed between dietary chloride intake per body weight (mg/kg/day) and body weight ($r = -0.52$, $P < 0.01$). No significant correlation was observed between body weight and daily amount of diet (g/kg) nor chloride content in the diet (mg/g).

Case 1 was a 9-year-old neutered male mixed-breed dog evaluated for poor seizure control. The seizure frequency was 4 times/month at a KBr dose of 30 mg/kg/day. Calculated from the ingredients label, its dietary chloride intake was 543.7 mg/kg/day. Measured using the method previously described, the serum bromide concentration was less than 0.1 mg/ml. Utilizing the KBr-Cl- intake formula, the expected serum bromide concentration was less than 0 mg/ml. The diet was changed to a commercial regular maintenance diet checking that the dog did not have urolithiasis by urine analysis and abdominal ultrasound. Four months after changing the diet, the serum bromide concentration had increased to 1.2 mg/ml. At this point, the seizure frequency decreased to once a month.

Case 2 was a 3.5-year-old neutered male miniature dachshund, presenting with a newly-occurring seizure. The dog received KBr with a dose of 20 mg/kg/day for 4 months. Calculated from the ingredients label, the dietary chloride intake was 70.9 mg/kg/day. Measured using the method previously described, the serum bromide concentration was 1.3mg/ml. At this serum

bromide concentration, seizures continued to occur. Utilizing the KBr-Cl- intake formula, the expected serum bromide concentration was 1.47 mg/ml. The difference between the actual serum bromide concentration and expected bromide concentration from the formula was 12%. To improve the seizure control and prevent severe seizures, the KBr dosage was increased for a target serum bromide concentration of 2 mg/ml. The KBr-Cl- intake formula gave an appropriate KBr dose for this concentration of 25 mg/kg/day. In order to correct the difference in actual bromide concentration and expected bromide concentration (12%) measured previously, the dog was medicated with 28 mg/kg/day ($25 \times 1.12 = 28$). Three months after changing the dose, the serum bromide concentration was 2.2 mg/ml and the dog was seizure free.

DISCUSSION

The aim of this study was to quantify the relationship between dietary chloride intake and serum bromide concentration, and improve seizure control in dogs on KBr. Our study provides the KBr-Cl- intake formula that describes the numeric relationship between dietary chloride intake and serum bromide concentration in dogs. To the authors' knowledge, this is the first study to report an actual numeric relationship between dietary chloride intake and serum bromide concentration in dogs. The KBr-Cl- intake formula was applied effectively to two clinical cases in this study. Our results suggest that it is important to consider the dietary content of chloride for KBr-treated dogs. The KBr-Cl- intake formula will contribute to improving seizure control by allowing the selection of KBr doses and appropriate diets by clinicians for dogs treated with KBr.

In this study, a positive correlation was observed between body weight and serum bromide concentration per dose, whereas a negative correlation was observed between body weight and dietary chloride intake. Since there was no correlation between neither body weight and daily amount of diet (g/kg) nor chloride content in the diet

(mg/g), these results indicate that dogs with lower body weight had slightly lower serum bromide concentrations than dogs with greater body weight regardless of their diet. One possible explanation is that there might be an endogenous factor affecting bromide excretion between different sizes of the dogs. Another possible explanation is that the results were influenced by the inclusion of only one dog with higher body weight, having high serum bromide concentration and low chloride intake, in this study. These results suggested that chloride might have a stronger influence in dogs with lower body weight or that it increases bromide excretion compared with dogs with higher body weight. We could not confirm this from our results. There was only one dog weighing more than 20 kg in this study. Ideally, including more dogs heavier than 20 kg would potentially have allowed for evaluation of body weight differences in the relationship between dietary chloride intake and serum bromide concentration.

In Case 1, the KBr-Cl- intake formula was applied to discover the cause of non-increased serum bromide concentration, revealing an expected serum bromide concentration of less than 0 mg/kg. This value suggested that the high dietary chloride intake enhanced serum bromide excretion, and serum bromide concentration was not maintained. In this case, changing the dog's diet resulted in an increased serum bromide concentration and seizure reduction. It is important to note that the KBr-Cl- intake formula cannot be applied to dogs with high chloride content of more than 435 mg/kg/day in the diet because the right side of the KBr-Cl- intake formula will be less than 0. Some dogs cannot discontinue high chloride diets because of concurrent conditions, for example, urolithiasis. Based on our results, clinicians must use caution when treating such dogs with KBr for seizure control.

In Case 2, the KBr-Cl- intake formula was utilized for KBr dose selection to achieve better seizure control. Adjustment was made to the dosage calculated from

the formula based on the previous serum bromide concentration measurement of this dog, resulting in better seizure control. Considering the two clinical KBr medicated cases, the KBr-Cl- intake formula was useful in the clinical setting.

Formulas for calculating the adequate dose of KBr for concomitant phenobarbital-KBr treatment and KBr monotherapy in dogs have been reported previously.¹³ These formulas are useful for decision-making in dogs treated with KBr, but cannot be applied in some cases. The problem is that chloride intake has not been considered in spite of the evidence that high contents of chloride decrease the serum bromide concentrations in dogs. Hence, if the dietary chloride intake is available, using the KBr-Cl- intake formula is more useful for dose selection. However, the formulas reported by Bhatti *et al*¹³ remain useful because the amount of chloride intake is not available in every case. Our two cases emphasized the importance of considering chloride intake in dogs on KBr and the usefulness of the KBr-Cl- intake formula.

A limitation of this study was the small sample size. There was only one dog weighing more than 20 kg in this study. Including more dogs with greater body weight might have allowed for evaluation of body weight differences in the relationship between chloride intake and serum bromide concentration. Another limitation of our investigation is that the accuracy of the KBr-Cl- intake formula for cases with renal failure and on diuretics is unknown. Although the excretion pathway of bromide is not fully elucidated, diuretics might increase bromide excretion by inhibiting bromide reabsorption from the chloride transporters at renal tubules. In one case report, diuretics were given to dogs with KBr intoxication in order to reduce serum bromide concentration.²⁰ Additional research is needed to evaluate the availability of the KBr-Cl- intake formula in dogs with renal failure and medicated with diuretics.

CONCLUSIONS

A strong negative correlation was observed

between dietary chloride intake (mg/kg/day) and the serum bromide concentration per dose ($\mu\text{g/ml}$ per mg/kg) ($P < 0.01$). The KBr-Cl- intake formula was established based on these two parameters. Our results suggest the importance of considering the dietary content of chloride for KBr-treated dogs and may also allow the selection of KBr doses and appropriate diets by clinicians for dogs treated with KBr.

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Conflict of Interest Statement

None of the authors has any personal, professional or financial relationships that could inappropriately influence or bias the content of the paper.

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