CASE STUDIES IN POTASSIUM BROMIDE

These case studies were shared by Dr. Simon Platt.

Bromide (Br) was first used in the treatment of human epilepsy in 1857. Although it is still used to treat specific types of refractory seizures in children, the use of Br in humans has decreased throughout the 20th century due to the availability of other anti-epileptic medications (AEMs).

The use of potassium bromide (KBr) was first reported in dogs in 1907 and now is one of several AEMS available to choose from for the long-term treatment of epilepsy. KBr is an affordable, relatively safe and effective AEM. Its prolonged half-life allows for convenient once or twice daily administration. KBr can be used as both a mono-therapeutic agent or in combination with other AEMs. Here we present two case scenarios that highlight the current use of KBr. Although research has found no support for the preferential use of this drug over phenobarbital as a first choice AEM, these cases will hopefully highlight how we often do use this effective medication.

In Dr Platt's free online CE in collaboration with VetEducation[™], additional insight can be gleaned about the use of potassium bromide and other supporting case studies. To view the CE course, visit: <u>http://bit.ly/PLATT2019</u>.

CASE 1 – THE LIVER CONCERN



The Patient and Its Story - An 8-year-old neutered male mixed breed dog presents with lethargy, inappetence and some weight loss. The dog was diagnosed with epilepsy 4 years ago. Based on a lack of neurologic dysfunction becoming evident over the period since this time, the diagnosis for the seizures is presumed to be idiopathic epilepsy. The dog has been treated with 2.5 mg/ kg phenobarbital twice daily since the seizures began. The seizures are generalized tonic-clonic in nature and have been occurring with a frequency of approximately two per month over the last year. In between the seizures the dog has been considered healthy until the last couple of weeks, when in addition to the above signs the dog's thirst seems to also have increased.

No physical or neurologic abnormalities are detected on the exam, besides a mental dullness and a slightly enlarged liver on abdominal palpation. Hematology results revealed a mild non-regenerative anemia; serum chemistry revealed marked elevations of liver enzymes (ALT 325 U/L {10-118};

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Figure 1. Hepatomegaly is seen on an abdominal radiograph.

ALP 12,452 U/L {20-150}), a low albumin level (2.5 g/dL {2.5-4.4}) and an elevated BUN (43 mg/dL {7-25}). On account of the fact that these liver enzyme elevations may just be induced by the phenobarbital and not indicative of a functional liver problem, a functional bile acid test was performed and revealed markedly elevated post-prandial levels (132 μ mol/L{>25}). Serum phenobarbital levels were within the therapeutic range but were towards the high end (39 μ g/mL{15-45}). Radiographs of the abdomen confirmed a large liver with rounded borders (see Figure 1 on page 2). The owners could not afford to pursue abdominal ultrasonography and so the hepatic dysfunction

Of two commonly used options for seizure control in dogs with liver function concerns, potassium bromide and levetiracetam, only the use of potassium bromide has been proven to be an effective monotherapy in dogs. based on the bile acid results was presumed to be related to the phenobarbital administration.

The Problem – The dog has a presumed liver dysfunction related to phenobarbital administration but has a consistent and concerning seizure frequency which needs to be addressed.

The Solution – The dog needs the phenobarbital withdrawn, with a rapid alternative used in its place. Potassium bromide and levetiracetam are the usual drug considerations for seizure control in dogs with liver function concerns. However, of these two options, only the use of potassium bromide has been proven to be an effective monotherapy in dogs, whereas levetiracetam is preferred as an adjunctive medication. The half-life of potassium bromide is long, which practically means that if administered on a once daily basis it will take up to three months to reach steady-state, a point at which we can start to rely consistently on the effect of this drug. At higher daily doses than usually recommended, this waiting period can be improved upon; in one study, the majority of dogs administered KBr at 30 mg/kg every 12 h (60 mg/kg/day, which is a higher dosage than routinely recommended for clinical use) reached 75% and 90% of apparent steady-state concentrations by 30 and 60 days, respectively (March et al., 2002). In our dog's case, 3 months is too long to wait. So, a decision must be made to load the dose of KBr. Oral loading can be performed by administering KBr at 625 mg/kg divided in eight or more doses over 48 h, or 125 mg/kg/day divided in three to four daily administrations

Pertinent blood parameters	Case results	Reference range
ALT	325	10-118 U/L
ALP	12,452	20-150 U/L
Albumin	2.5	2.5-4.4 g/dL
BUN	43	7-25 mg/dL
Pre-prandial bile acids	12	<25 μmol/L
Post-prandial bile acids	132	<25 μmol/L
Phenobarbital	39	15-45 μ g/mL

for 5 consecutive days. Loading can be associated with adverse effects (e.g., nausea, vomiting, diarrhea, sedation, ataxia and pelvic limb weakness, polydipsia, polyuria and polyphagia) and hospitalization of the animal is recommended (Trepanier, 1995). Where possible, phenobarbital should be withdrawn in a tapering fashion, reducing the dose by approximately 25% every 2 weeks to reduce the chance of adverse effects. Regardless, loading with KBr will get it to steady state after 5 days so it should then be an effective and reliable anti-convulsant option. KBr has been shown to be effective as a sole AEM in epileptic dogs. In a recent double-blinded, randomized, parallel, clinical trial in dogs, KBr monotherapy resulted in a significant decrease in seizure number and severity and an increase in seizure interval at study end (6 months), compared with baseline. In addition, seizure duration decreased over time, although not significantly (Boothe *et al.*, 2012). Seizure activity was eradicated in 52% (12/23) and decreased by >50% in 65% (15/23) of KBr-treated dogs.

CASE 2 – THE CLUSTER BUSTER



The Patient and Its Story – A 3-year-old, spayed female collie-cross dog was documented with an onset of generalized seizure activity approximately 12 months ago. A complete investigation including MRI and CSF tap was normal, compatible with a diagnosis of idiopathic epilepsy. The initial frequency of seizures was reported to be approximately 1-2 times a week. Following administration of phenobarbital at 3 mg/kg twice daily, the seizures reduced in frequency to 1-2 times a month. Recently, however, the seizures have started to increase to a 3-4 times a month frequency. Additionally, there have been 2 days

A dog is considered to have cluster seizures if they experience more than two seizures per day.

over the last 3 months where cluster seizures have been noted, with 5-6 seizures occurring in one day!

The dog's general health is considered stable with no abnormalities noted. Physical and neurologic examinations were normal. Hematology was within normal limits but serum chemistry revealed a moderately elevated ALP (763 U/L $\{20.150\}$). Serum bile acids were normal both pre- and post-prandially and so the elevation of this enzyme was considered to be due to induction by the phenobarbital rather than representative of liver dysfunction. Serum phenobarbital concentration was 23 µg/mL (15-45).

The Problem – The overall seizure frequency is considered high with an optimal aim of one seizure every three months or better, where possible. Additionally, the presence of cluster seizures (>2 seizures / day) is a major concern for the potential of further loss of seizure control.

Potassium bromide given as an adjunct to phenobarbital has been shown to improve the control of of cluster seizures.

The Solution – While better long-term control could be attained with an increased phenobarbital dose, which is feasible based on the current serum level of this drug, the addition of a second drug would improve the chance of getting to an optimal level of control. Choosing an adjunctive drug which has demonstrated efficacy in the treatment of cluster seizures would be valuable. Potassium bromide has been shown to improve the control of cluster seizures, a property which has not been demonstrated by the addition of other drugs such as levetiracetam or zonisamide.

An animal that experiences one day of seizures per year may be considered fairly well controlled, but if the seizures occur in a flurry or cluster, this episode may result in a yearly visit to an emergency room or even hospital admission. The terms *acute repetitive seizures*, *cluster seizures*, *serial seizures*, and *flurry seizures* describe a condition characterized by multiple generalized tonic, clonic or tonic-clonic seizures or multiple focal seizures with or without secondary generalization in patients with epilepsy occurring over a relatively brief period of time. Acute intervention with benzodiazepines may abort such seizures and decrease adverse outcomes. Clusters have been related to a higher overall seizure frequency, medication-resistant epilepsy and a higher mortality than that seen in patients with epilepsy without clusters.

In this dog, an elevation of the phenobarbital dose by 25% of what is currently being given, and either addition of potassium bromide at a maintenance dosage of 30 mg/kg once daily or a loading dose of KBr would be recommended. When KBr loading is needed in dogs that are unable to take oral medication (e.g., status epilepticus, severe sedation and/or severe post-ictal phase) KBr can be administered rectally using the same regimen as described above. While short-term approaches may also be necessary for the owner to use at home when the dog experiences multiple seizures in one day, the long-term control of clusters necessitates a maintenance drug approach.

Treatment and dosages should be based on the individual animal's response to therapy and to minimize side effects. This may include monitoring blood bromide levels and clinical signs. Not for use in cats. Use caution with chloride-containing medications and food.



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Dr. Simon Platt received his veterinary degree from the University of Edinburgh, Scotland, in 1992. Following that, he undertook an internship in Small Animal Medicine and Surgery at the Ontario Veterinary College at the University of Guelph and a two-year period in private practice in England.

Dr. Platt completed a residency in neurology and neurosurgery in 1998 at the University of Florida and afterward spent two years as an Assistant Professor of Neurology at the University of Georgia. In 2000, Dr. Platt returned to the UK where he was Head of the Neurology/

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Dr. Platt has authored or co-authored more than 190 journal articles and 50 book chapters and is the co-editor of three textbooks: BSAVA Manual of Canine and Feline Neurology; Small Animal Neurological Emergencies; and Canine and Feline Epilepsy: Diagnosis and Management.

