Management of canine epilepsy with phenobarbital and potassium bromide

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Seizures (or convulsions) are caused by an increased electrical activity of the brain. Epilepsy is a non-progressive, intracranial disease that produces intermittent seizures. Pharmacological control of epilepsy in the dog is begun if seizures occur more frequently than once a month, if more than one seizure occurs on the same day, or if the animal presents in status epilepticus (a life-threatening state of continual seizure activity). Additional circumstances to be considered before beginning treatment should include: the patient's environment and use, the owner's compliance and ability to medicate the animal, and the owner's acceptance of seizure episodes.

Owners must understand that their pet will continue to have seizures while on medication; that the goal of therapy is to decrease the frequency, duration, and severity of the seizures; that approximately 20% to 50% of canine epileptics will never be controlled with medical management (large breeds of dogs are particularly difficult to regulate); that multiple dosage regimens may need to be tried before the correct one for their pet is found; and that the medication will usually be required for the rest of the pet's life. Abrupt withdrawal of medication may precipitate seizures.

The most common drugs used in the medical management of canine epilepsy are phenobarbital and potassium bromide.

Phenobarbital is the primary drug used in the management of epilepsy because of its efficacy, low cost, and minimal toxicity. It increases the seizure threshold and decreases the electrical activity of the seizure focus by potentiating gamma-aminobutyric acid (GABA), the inhibitory neurotransmitter in the central nervous system (CNS).

After oral administration, peak phenobarbital plasma concentrations occur in 4 to 8 h. Phenobarbital is widely distributed into tissues, but because of its lower lipid solubility, it does not penetrate as rapidly as other barbiturates into the CNS. After IV injection, therapeutic concentrations in the CNS are reached in 15 to 20 min. Phenobarbital is primarily metabolized by the liver, with only 25% excreted as unchanged drug by the kidney. Reported elimination half-lives are 48 to 144 h in humans and 37 to 75 h (average 53 h) in dogs.

Phenobarbital is a well-known inducer of hepatic microsomal P-450 enzymes. Induction of microsomal enzymes enhances biotransformation of other drugs, resulting in a diminished pharmacological effect for the concurrently administered drug (e.g., digoxin, glucocorticoids, phenylbutazone, anesthetics). In contrast, drugs that are inhibitors of hepatic microsomal enzymes (e.g., chloramphenicol, tetracyclines) may inhibit phenobarbital metabolism and cause toxicity.

Side effects of phenobarbital are seen soon after starting therapy. Typical signs include sedation, polyphagia, polyuria/polydipsia, and behavioral changes. Pharmacokinetic and pharmacodynamic tolerance develop after 10 d to 2 wk of therapy, when side effects will diminish. Elevated hepatic enzymes (alanine aminotransferase(ALT), alkaline phosphatase(ALP)) can occur after chronic therapy without hepatic disease. Clinicians should be concerned about phenobarbital toxicity if the ALT is disproportionately elevated in comparison to the ALP, or if there are concurrent elevations in bile acids or other signs of hepatic disease. Serum concentrations of liver enzymes should be evaluated every 6 mo for dogs on chronic therapy.

Daily phenobarbital doses of 4 to 16 mg/kg BW/day are recommended. Initially, the full dose is usually divided into twice daily doses to minimize side effects and peak-trough fluctuations. In some patients, once a day dosing may be effective. Therapeutic plasma concentrations in dogs are much higher than those considered desirable in humans (dogs: 70 to 170 μmol/L, humans: 43 to 108 μmol/L). Plasma phenobarbital concentrations should be measured 6 half-lives (approximately 2 wk) after beginning the therapy. A trough plasma sample should be collected 8 to 12 h after an oral dose. An algorithm may be used as a guide in adjusting phenobarbital dosage (Figure 1).

Potassium bromide (Kbr) is the oldest and, chemically, the simplest of the anticonvulsant drugs. Although it is rarely used in humans due to its toxicity, bromide has recently become popular as a second anticonvulsant drug in dogs that continue to have seizures despite adequate phenobarbital concentrations. Bromide replaces chloride in all body fluids and stabilizes neuronal cell membranes by interfering with chloride transport and potentiating the effect of GABA. Bromide is synergistic with other drugs with GABA-ergic activity, such as phenobarbital, in raising the seizure threshold.

Potassium bromide is well absorbed from the gastrointestinal tract in dogs, with peak absorption in 1.5 h. Maximum bromide concentration in CSF occurs 2 h after oral administration. The elimination half-life is extremely long (24 d), therefore it takes approximately

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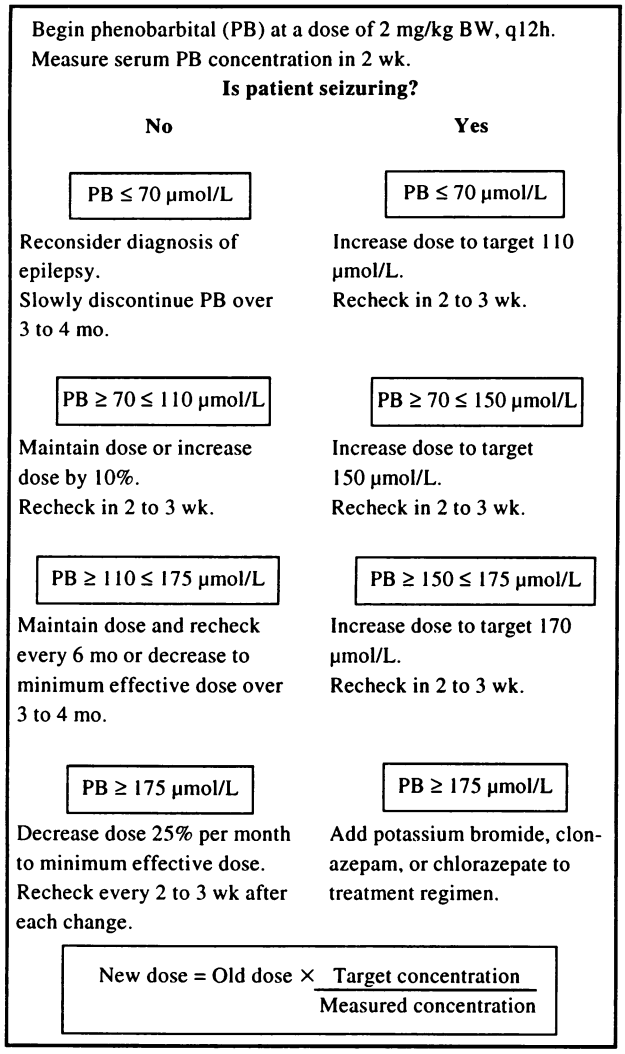

Figure 1. Algorithm for management of idiopathic epilepsy with phenobarbital

4 mo to achieve steady-state concentrations. Bromide is eliminated by the kidneys. Because it does not undergo hepatic metabolism, bromide does not affect hepatic enzymes and, therefore, is useful in dogs with liver disease.

Bromide toxicosis (bromism) may be seen if serum concentrations exceed the therapeutic range. Neurological signs of bromism include lethargy, generalized ataxia, disorientation, and delirium. Some animals may show signs of sedation for the first 3 wk of therapy. Other common side effects include polyuria/polydipsia, erythematous dermatitis ("bromide rash"), conjunctivitis, nausea, and anorexia. Sensitivity may be affected by the dog's physical condition, food and salt intake, hydration, vomiting, diarrhea, or renal insufficiency.

The clinician should consider the addition of bromide to anticonvulsant therapy when phenobarbital control is insufficient. Guidelines for Kbr addition are as follows: 1) seizure cause is not identified; 2) phenobarbital has been administered for at least 3 mo and a steady-state trough concentration of 130 µmol/L has been achieved; 3) the number and severity of the seizures have remained unchanged for at least 3 mo, despite therapy with phenobarbital and other anticonvulsant drugs; or 4) there is evidence of hepatotoxicity from previous anticonvulsant therapy. A majority of dogs will have decreased seizure activity when Kbr is added to phenobarbital therapy. Frequently, there is a decrease in seizure intensity and a change to a less severe type of seizure.

Potassium bromide can be purchased from a chemical supply company (VWR Scientific, 9527 49th Street, Edmonton, Alberta) and formulated in double distilled water by a pharmacist. The recommended starting dose is 10 mg/kg BW, q12h, given in food. This allows the dog to gradually adapt to the cumulative sedative effects of phenobarbital and bromide, while maintaining high steady-state trough concentrations. The therapeutic range for bromide is considered to be 10 to 20 mmol/L. Bromide concentrations should be monitored at 30 d, 120 d, and every 6 mo after initiating the therapy. Therapy must be individually tailored, as serum bromide concentrations vary among dogs and each dog adjusts to bromide differently.

Once bromide reaches steady-state serum concentrations in the therapeutic range, the clinician can attempt to decrease the total daily phenobarbital dose. Further reductions in the phenobarbital dose can be attempted if the dog remains seizure- free for 6 mo. In some dogs, the addition of Kbr allows phenobarbital doses to be decreased by as much as one half. Some dogs can be successfully maintained on bromide therapy alone.

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Therapeutic drug monitoring for bromide is available from the Clinical Pharmacology Service of the Ontario Veterinary College by contacting Dr. Peter Conlon (519 823-8800, ext. 4950). Practitioners should submit 1.5 to 2.0 mL of serum in glass vacutainers, shipped cold, to: Room 2619, Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1.