

Phenobarbital and Potassium Bromide Therapy Which one do I use? Or is it both?

Robin Levitski-Osgood, DVM, Diplomate ACVIM (Neurology)

Treating seizures

Obtaining a diagnosis = proper treatment

Treat acquired epilepsy based on the diagnosis

- Congenital or anomalous- appropriate drug therapy (diuretics, steroids) +/- surgery
- Brain tumor- steroids, anticonvulsants, surgery and/or radiation
- Inflammatory/Immune/GME- steroids, +/- immunosuppression, +/- radiation
- Infectious- appropriate antibacterial or antifungal drug, +/- steroids
- Trauma- diuretics, steroids, anticonvulsants, +/- surgery

Idiopathic, inherited, or familial epilepsy is very difficult to confirm in most breeds. If the blood work, imaging and spinal fluid analysis are normal, then all other causes of seizures have been ruled out and a diagnosis of idiopathic epilepsy is made.

The term “idiopathic” basically means that no specific cause can be identified for the seizures. Anticonvulsant therapy is generally necessary to manage them. Most large dogs tend to kindle and require therapy if they seizure more than once every 3 to 4 months. Smaller dogs are often allowed to seizure once a month before therapy is started. Dogs that have cluster seizures should be treated. The deciding factors are the owners, the progression of the seizures’ severity and frequency, and the post-ictal phase.

Almost all patients with epilepsy need some form of anticonvulsant therapy at some point in time. **NO DRUG IS EFFECTIVE IN ALL CASES.**

Foundation of anticonvulsant therapy

- Appropriate work up
- Knowledge of pharmacokinetics of the drugs used
- Serum drug levels
- Therapeutic ranges are only guidelines-not normal values!
- Multiple drug usage - paradoxical intoxication
- Illnesses
- Elderly or pregnant patients - decrease proteins can alter the effect of some drugs

The faster serum drug concentrations are reached, the better the success. It is best to start with higher dosages or a loading dose.

Guidelines for starting anticonvulsant therapy

DRUG

- Always start with ONE drug (either PB or KBr)
- Phenobarbital 4 mg/kg PO BID
- KBr 45 mg/kg PO SID
- Discuss the clinical side effects of the anticonvulsant with the owners
- Discuss realistic expectations of seizure control with the owners

LEVELS

- Monitor the serum drug concentration after starting the anticonvulsant or after changing the dose unless you have loaded them.
 - 3 to 4 weeks for Phenobarbital
 - 6 to 8 weeks for KBr

FOLLOW UP

- Monitor the dog's clinical signs after starting anticonvulsants.
- Screen for concurrent conditions that may lower the seizure threshold or predispose the animal to seizures (intact dog-hormonal, hypothyroidism, allergies).
- Seizures greater than 1 time a month
 - Check a current drug level and increase the drug as needed until the serum drug concentration is at the high end of the therapeutic range.
 - If the seizures still continue greater than once a month and the serum drug concentration is at the high end of the therapeutic range, then it is time to add a second anticonvulsant to the protocol.
- Seizures that occur every 2 months or longer
 - If the seizures are well controlled (less than 1 a month), then continue with the dose of anticonvulsants and recheck serum drug concentrations and chemistry panel every 6 months to 1 year.

Common problems with anticonvulsant therapy

- The medication is started at too low of a dose
- The medication is changed too quickly before the therapeutic range is reached
 - The therapy can be changed only after the highest possible level is reached
- A second drug is added before therapeutic levels are reached for the first drug
 - Monotherapy is superior to polytherapy
- Phenobarbital is discontinued before the 2 week adjustment period due to side effects (lethargy, ataxia, recumbency)
- Change in administration of the drug
- Unrealistically high expectations of anticonvulsant therapy
- Drug interactions (antibiotics, antacids, cardiac drugs, steroids, theophylline)
- Renal or hepatic diseases

PHENOBARBITAL

Dosage and therapeutic levels

- **4 mg/kg PO BID** to get the dog to a serum drug concentration between 26-35 ug/ml.
- Steady state of the drug is reached in about 14 to 28 days (3 to 4 weeks).
- The therapeutic range in the dog is 15-45 ug/ml. This is just a range—NOT a normal value. The dose is adjusted based on the serum drug levels and the dog's clinical signs. There is a linear correlation between the dose and the serum drug level.
- You can give the same dose IM or IV if the dog is hospitalized and unable to take oral medications.
- Cats: 3 mg/kg PO BID. Cats tend to have higher serum PB levels than dogs at the same dosage.
 - Small to medium cats- 7.5 mg PO BID
 - Large cats 15 mg PO BID
 - Extra large cats 22.5 mg PO BID

Side effects

- The major side effects include sedation, polydipsia, polyuria, and polyphagia.
- PB is suspected to be hepatotoxic. Elevations of liver enzymes are common, but do not necessarily mean decreased liver function. Very high elevations can occur.
- Rarely, hematologic abnormalities (neutropenia, thrombocytopenia, anemia) have been reported to develop 2- 6 months after initiating treatment. CBC values are reported to return to normal within 7- 21 days of discontinuing the drug.

Monitoring

- Serum levels of PB are performed 3-4 weeks after every dose adjustment and every 6 months to one year after maintenance is achieved.
- Serum level of PB can be measured at any time during the day as the difference between pre and post pill levels is minimal.
- A chemistry panel is performed once a year if the animal is well controlled or sooner if there are problems.
- Pre and post bile acids should be evaluated if the serum cholesterol, albumin, or total protein are decreased or if you suspect the dog has decreased liver function.
- A CBC can be performed monthly or every 2 months for the first 6 months after starting PB or if there are clinical signs relating to bone marrow suppression.

Metabolism and MOA

- Phenobarbital is metabolized by the liver.
- Mechanism of action: Phenobarbital binds to GABA receptor at a specific barbiturate binding site. In the presence of GABA, the chloride channels are open for longer period of time and hyperpolarization occurs (the inside of the cell becomes more negative). PB also decreases the effects of glutamate, an excitatory neurotransmitter, and blocks the response to NMDA.

Other

- Drug interactions can be encountered. Some drugs potentiate the effects of PB (chloramphenicol, cimetidine).
- Therapy can be weaned if the patient has had no seizures within 6-12 months. Decreasing the drug by 20% every 2-6 months is recommended while monitoring for breakthrough seizures. Most animals will have more seizures once the drug is decreased enough.

POTASSIUM BROMIDE

Dosage and therapeutic levels

- **45 mg/kg PO SID** (30-90 mg/kg PO SID)
- Loading dose: 400-600 mg/kg divided into 4 doses over 24-48 hours.
- OR 450-600 mg/kg over 5 days to reach a target concentration of 1.5 mg/ml of serum bromide.
- The therapeutic range of bromide in the serum is 1000 to 3000 ppm (1-3 mg/ml). This range is 810-2400 ppm (0.8-2.4 mg/ml) when the patient is also on PB. Higher concentrations may be needed.
- Most dogs on single agent KBr need serum drug concentrations > 2000 ppm.
- You can go above the therapeutic range if that is the dose needed to achieve seizure control, and the dog is not showing signs of toxicity.

Side effects

- **Side effects** are rare. GI irritation, sedation, paraparesis and ataxia have been noted. In people, GI signs, rashes, and emotional disturbances are noted. The idiosyncratic psychosis reported in human is difficult to document in animals.
- Whether or not KBr toxicity or potentiation of PB exists is uncertain but some patients on both drugs have shown more severe side effects.
- Avoid in pregnant animals.
- Adding salt to the diet or a NaCl diuresis can be used to treat a dog with signs of bromide toxicity. Use short term (<12 hours) saline diuresis at maintenance fluid rates. Watch for seizures as the KBr serum concentrations decrease rapidly.
- Feline asthma. Take thoracic radiographs prior to starting a cat on bromide. Have owners monitor for signs of respiratory disease. Discontinue the KBr and repeat thoracic rads if respiratory signs occur.
- Dermal changes. Subcutaneous nodules and hyperkeratosis of the nose. Not very well documented.

Monitoring

- Serum concentrations of KBr can be measured at any time of the day.
- Serum levels are done 6-8 weeks after the drug is started or after an increase in dose.
- Every 6 months to once a year after maintenance is achieved.

Metabolism and MOA

- KBr is **not metabolized**. It is excreted by the kidneys.
- Diuresis and high chloride diets will markedly lower serum bromide concentrations.
- The mechanism of action depends on the small size of bromide (Br⁻) compared to chloride (Cl⁻). The bromide ion replaces the chloride and enters the cell faster, making the inside of the cell more negative and less likely to discharge.
- The half life is approximately 23-27 days in the dog. Therefore, levels are not stable for about 4 to 5 months. Because toxic levels can be reached sooner, the first check should be performed 6 weeks after initiating therapy.
- Half-life in cats is shorter-- 10 days.

Other

- KBr has been shown to be effective in improving seizure control in 72% of epileptic dogs (greater than 50% reduction in seizures).
- Recommend putting the KBr on a piece of bread and feeding to the dog before their meal.
- Compounding pharmacies can formulate liver or beef flavored KBr for cats.
- Hyperchloremia is noted on the chemistry panel as some automated analyzers read Br as Cl.