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D I A G N O S T I C S

# News

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## ANTICONVULSANT THERAPY

As many Antech clients care for patients that require anticonvulsant therapy, the following summary addresses use of phenobarbital (Phb) and/or bromide (Br), and the laboratory monitoring of therapeutic drug levels.

### PHENOBARBITAL

Phb is the most commonly used anticonvulsant for controlling seizures in dogs, although side-effects may occur especially with long term use.

### ADVERSE EFFECTS

It is well known that Phb induces increased liver enzymes (SAP, ALT) in most dogs, but rarely does so in cats. Phb can also reduce serum albumin and cholesterol with chronic use, but overt hepatic failure (jaundice, cirrhosis, encephalopathy) is uncommon. The mechanism of hepatic failure is unclear, but is likely a dose- and duration-dependent toxicity. Reducing the dose of Phb will reduce abnormal liver enzyme and/or bile acid levels in most dogs. Bromide treatment may be required in those cases to maintain seizure control.

Phb treatment can alter thyroid and low-dose dexamethasone suppression (LDDS) tests. Phb is associated with decreased total serum T4 and Free T4, but normal T3 and normal or increased TSH concentrations. This may be due to such factors as the increased clearance of T4, increased biliary excretion of T4 as bile flow increases, and increased peripheral deiodination of T4 to T3. Thus, while Phb treatment may mimic hypothyroidism biochemically, the patient should not appear clinically hypothyroid, unless there is concomitant hypothyroidism.

Phb also enhances the clearance of dexamethasone, which may lead to a false positive (escape from suppression) on LDDS testing. However, Phb does not affect the cortisol response to ACTH stimulation or endogenous ACTH concentrations. Therefore, when testing for Cushing's disease in dogs, receiving Phb, the ACTH stimulation rather

than LDDS test should be used. Dogs receiving mitotane (Lysodren®) as well as Phb may require higher loading and maintenance doses of mitotane as Phb increases its elimination.

In rare instances, blood dyscrasias can result from Phb use (eg. thrombocytopenia, neutropenia, anemia). The underlying mechanism is unknown although it could involve deranged folate metabolism (seen with Phb treatment in humans), drug-induced immune-mediated disease, or direct marrow toxicity.

### DOSAGE

Phb should be given BID (q. 12 hours) in most dogs, and is given or needed TID (q. 8 hours) much less commonly. The elimination half-life is much greater than 12 hours in most dogs, and so levels are well sustained throughout a 12 hour period.

### MEASURING PHB LEVELS

It is commonly recommended to measure serum Phb concentrations at specific times, either just prior to the next dose (trough) or at 4 to 8 hours after dosing (peak). However, recent data indicate that once steady state concentrations have been reached (2 to 3 weeks after beginning treatment or after a dosage alteration), peak and trough Phb concentrations are not significantly different. Thus, in most dogs, only a single sample is required for Phb therapeutic drug monitoring and the timing of sample collection in relationship to dosing has little effect on clinical decisions.

Serum separator gel tubes (SST) should **not** be used for Phb measurements or for any therapeutic drug monitoring, as the drug absorbs to the gel giving falsely low serum drug concentrations.

The therapeutic range for serum Phb concentrations is 15-45 ug/mL. A recent rise in Phb level without an increase in dose may signal the onset of liver failure, and should be followed up with bile acids testing.

# ANTICONVULSANT THERAPY (cont'd.)

For dogs receiving KBr and Phb, less Phb may be required to control seizures and 20% or more of dogs started on KBr can be taken off Phb altogether.

## BROMIDE

Although potassium bromide (KBr) is the most commonly used form, sodium bromide (NaBr) can be used interchangeably with equivalent safety and efficacy.

KBr and NaBr are safe and effective drugs for controlling seizures in dogs, but are not approved drugs (available for investigational use only). Pet owners should be informed of this before Br is prescribed.

Br competes with chloride for transport across the neuronal cell membrane, causing hyperpolarization of the cell membrane and thus raising the seizure threshold. Br is absorbed orally and is eliminated by the kidneys. The half-life is approximately 24 days (dog) and 10 days (cat).

Br is indicated for use in combination with Phb in dogs in which seizures are not well controlled with Phb alone. Br also may be used as the sole anticonvulsant drug in dogs when Phb is contraindicated because of its potential hepatotoxic effects. Br is currently being evaluated for use in cats.

## PRECAUTIONS

Common adverse effects seen with Br or Phb + Br administration include ataxia, transient sedation, polyuria/polydipsia, and polyphagia. Br can cause gastrointestinal upsets. Dividing the daily dose and administering it with food may help to avoid GI side effects. Br should be used with caution in dogs with renal insufficiency, and safety

during pregnancy and lactation has not been established.

Br toxicity is uncommon, although it may occur in dogs with renal insufficiency or those on a high dose of Br. Signs of Br toxicity include ataxia, sedation or stupor, and muscle spasm. Reducing the dose by 10% to 25% is usually adequate to resolve clinical signs. If the dog is stuporous because of acute overdose, gastric lavage should be performed; however, this will remove Br only from the stomach. Diuresis with 0.9% sodium chloride will help lower serum Br levels.

## DRUG INTERACTIONS

Diuretics increase Br excretion and lower serum Br levels. Diets high in salt or chloride will increase Br elimination and result in poor seizure control.

Br and chloride compete for renal tubular reabsorption; increased dietary chloride will cause increased urinary excretion of Br.

## DOSAGE

The recommended daily maintenance dose of Br is 30 to 40 mg/kg orally; the pharmacokinetics of rectal and parenteral administration in dogs are currently under investigation. A loading dose of 450 to 600 mg/kg, usually divided over 5 days, can be used initially if rapid seizure control is desired. During these 5 days, it is also important to give the maintenance dose; thus, a typical loading protocol would be 120 mg/kg/day plus 35 mg/kg/day for 5 days. Serum Br levels are measured within the first few days after completion of the loading dose. Side effects may be more likely during these 5 days. Weaning from Phb (if required) should be done after 2 to 3 months of Br maintenance therapy or after 1 to 2 days of the Br loading dose.

Therapeutic drug monitoring is essential and should be performed after loading and 2 to 3 months of maintenance therapy, loading, or any change in dosage. Even when the patient is doing well, serum Br levels should be checked every 6 months.

Therapeutic serum levels for most dogs are 1 to 3 mg/mL but may vary depending on the animal's tolerance. The timing of blood collection for determining Br concentration in relation to administration of the medication is unimportant, because of the long half-life of Br. Use of SST for blood collection should be avoided as it may falsely decrease Br concentration.

Br is available in powder form from any chemical supply company (request medicinal or American Chemical Society [ACS] grade). Many pharmacists compound Br into liquid solutions, capsules, and chewable tablet forms.

In powder or capsule form, Br should be stored at room temperature. Once formulated into a liquid solution, it should be kept refrigerated and discarded after 6 months.

## DRUG MONITORING\*

### PHENOBARBITAL

Specimen

Requirement . . . . . Serum (0.25 ml)

Turnaround Time . . Daily (Mon.-Sat.)

### BROMIDE

Specimen

Requirement . . . . . Serum (0.25 ml)

Turnaround Time . . Daily (Mon.-Sat.)

Please call laboratory for current test codes and pricing.

\*Do not use serum separator gels tubes for measuring these drug levels.

References: Boothe, Vet Clin N Am 28(2): 411-448, 1998; Trepanier, Proc 17th ACVIM, 1999, pp 268-269; Ducoté, Compendium, July 1999, pp 638-639.

## LAB TIPS

Occasionally, biopsy samples larger than the biopsy jars are taken. However, it is not helpful or safe to submit the entire sample in formalin. With shipping regulations for air and ground transportation becoming stricter, and with formalin classified as a hazardous chemical, it is becoming difficult to ship large containers of formalin.

Also, from a medical standpoint, large samples immersed in formalin do not fix deeper than 1/4 inch into the tissue. The unfixed center becomes autolytic and nondiagnostic. The best approach would be to take several small sections from the larger mass and submit those in smaller formalin containers. Some larger masses can be sliced serially to allow for better fixation. The only exception to this are intact hearts, which should always be submitted whole, without prior dissection.

## FRUCTOSAMINE AND GLYCOSYLATED HEMOGLOBIN

Fructosamines are serum proteins (albumin and others) that have undergone nonenzymatic, insulin-independent glycosylation. Serum fructosamine concentration is proportional to the blood glucose concentration over the lifespan of the glycosylated protein being measured. The lifespan of albumin in dogs (and presumably in cats) is 1-2 weeks. Thus, the serum fructosamine concentration should reflect the mean blood glucose concentration over the preceding 7-10 days.

Likewise, glycosylated hemoglobin (Hb) is produced from an irreversible, nonenzymatic, insulin-independent binding of glucose to Hb. In this way, it is an indirect assessment of the mean blood glucose for the preceding several weeks, depending on the half-life of the red blood cells (RBC). Since RBC lifespan in dogs is 120 days, the Hb reflects the mean blood glucose over the last 8-12 weeks, while in cats it reflects the mean blood glucose over the preceding 5-6 weeks (feline RBC half-life of 66-78 days).

Both fructosamine and glycosylated Hb concentrations are generally lower in normal animals than diabetic animals. Furthermore, diabetics with good glycemic control (as assessed by mean blood glucose concentrations and clinical signs) have lower fructosamine and glycosylated Hb levels than animals with poor glycemic control; and both values tend to decrease as glycemic control improves. In addition, while cats with stress hyperglycemia have significantly higher blood glucose concentrations than normal cats, there is no difference between the two groups when evaluating fructosamine or glycosylated Hb levels.

### Test Limitations

Although these 2 tests tend to reflect blood glucose levels, there is some overlap between diabetic and non-diabetic animals as well as between animals with good and poor glycemic control. Even cats with good glycemic control tend to have fructosamine levels higher than the normal range. Thus, it is always necessary to evaluate these tests in light of other clinical signs.

Changes in serum albumin levels

will alter fructosamine levels. Low concentration of albumin or plasma proteins will result in lower than expected fructosamine concentrations while a low rate of protein turnover can increase serum fructosamine levels. In a similar manner, anemia will markedly decrease the glycosylated Hb concentration.

A recent study compared both tests and concluded that fructosamine concentration reflected glycemic control better than glycosylated Hb and more accurately reflected changes in glycemic status. In addition, measuring glycosylated Hb requires specialized techniques so that most laboratories send the samples out for measurement which increases both the cost and turn around time.

Although an elevated fructosamine or glycosylated Hb level may indicate less than ideal glycemic control, these values alone cannot tell the clinician how to alter the insulin treatment in order to improve control. For example, a dog that is receiving too little insulin will have a high fructosamine level, but so will a dog receiving too much insulin. The overdose can lead to the Somogyi effect and the subsequent hyperglycemia will lead to an elevated fructosamine concentration.

### Clinical Use

Glycosylated Hb is probably most useful as an indicator of glycemic status in animals with well-controlled diabetes. Either test can be used to differentiate stress hyperglycemia from diabetes mellitus *when evaluated together with results of fasting blood glucose, urine glucose and clinical signs*.

Preliminary studies indicate that sequential evaluation of fructosamine concentration before and after use of insulin may be helpful in confirming changes in glycemic control.

Fructosamine concentration also can help differentiate cats with poor glycemic control from cats that have become fractious or stressed during determination of blood glucose curves. The best way to monitor an extremely fractious cat may be to anesthetize the animal and insert a jugular or other long catheter into the medial femoral vein with enough extension tubing to permit blood sampling without stressing the patient or clinic staff. This also allows for a good physical examination, blood and urine collection