Phenobarbital Utilization in Veterinary Practice

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Introduction

Seizure disorders are the most common neurological condition noted in small animal practice. Referral practices report that 1-2% of canine patients and 2-3.5% of felines present with seizure disorders.[1]

Treatment

Treatment is based on the overall disease process producing the seizure.

- If extra-cranial disease is found, that underlying cause must be treated to prevent further seizures. In some cases, anti-seizure medications may be utilized until the underlying disease is controlled.
- If intra-cranial disease is diagnosed or suspected, anti-epileptic drugs may be indicated. The decision to start using these medications is based on the following criteria:
    a) Seizure frequency is every 6 months or greater
    b) Cluster seizures – greater than 2 seizures in a 24 hour period
    c) Status epilepticus – severe seizure episodes, lasting longer than 5 minutes
    d) Owner's strong desire to treat seizures

An anti-epileptic medication should be chosen based on mechanism of action, reported efficacy, potential for adverse effects, drug interactions, frequency of administration and cost.

Phenobarbital (PHB)

Phenobarbital often serves as a first line medication for the treatment of primary seizures in dogs and cats.[1] It is a long-acting, barbiturate medication and a popular choice due to efficacy, availability, cost, dosing convenience, and safety when dosed and monitored appropriately. Seizures are controlled in 70% of dogs and most cats with PHB monotherapy.[2]

Mechanism of Action

PHB stabilizes neurons by acting on the GABA receptors. This increases the seizure threshold and reduces the spread of seizure activity.

Pharmacokinetics

PHB has a long half-life, and it takes 2-3 weeks to achieve blood steady state levels in dogs and cats.[3]

Reported Adverse Effects

Side effects can include sedation, ataxia, polyphagia, weight gain, polyuria and polydipsia (PU/PD), hepatotoxicity, bone marrow suppression and hyper-excitability.

- o Hepatotoxicty is usually avoided in an otherwise healthy patient when dosed in the therapeutic range.[4]
- o Sedation and ataxia typically subside after the first 10-21 days of therapy.[2]
- o Owners should be warned to refrain from over feeding their pet due to the side effect of polyphagia.
- o In addition, PHB increases the biotransformation of drugs metabolized by the liver, decreasing the effects of many medications that may be administered concurrently.
- o Drugs that inhibit microsomal enzymes may dramatically inhibit the metabolism of PHB, resulting in hepatotoxic levels.

Beginning PHB Therapy

An initial database should be performed prior to starting chronic PHB medication. PHB levels should be evaluated once steady state levels are achieved; this is generally recommended at 14 and 28 days initially. An appropriate starting dose is 2.5 mg/kg orally every 12 hours.[2]

Monitoring PHB Therapy:

1. PHB levels should be tested 2 weeks after starting treatment or 2 weeks after any change in dose or dosing frequency.[2]
2. Routinely perform PHB levels every 6 months along with a full liver panel and complete blood count to screen for bone marrow suppression and hepatotoxicity.[2]
3. Re-test PHB levels whenever 2 or more seizures occur between scheduled PHB evaluations.[2]

Additional Notes

- Drug levels should be obtained at the same time relative to the time the medication was administered for each sampling.
- While peak and trough levels have been discussed in past literature, trough levels only need to be considered if dosing is not every 12 hours, or if seizures tend to occur at the end of the 12 hour period, just before the next dose is due.
- Over time, PHB may induce hepatic microsomal enzymes increasing its own elimination and warranting a higher dose to maintain therapeutic levels.

Abaxis® VetScan® Phenobarbital Profile

The VetScan Phenobarbital Profile used with the VetScan VS2 Chemistry Analyzer provides comprehensive evaluation of PHB level and screening for hepatotoxicity for gold-standard patient care through the following analytes: alanine aminotransferase (ALT), albumin (ALB), alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen (BUN), gamma glutamyl transferase (GGT), phenobarbital (PHB), and total bilirubin (TBIL). Samples used can be heparinized whole blood, heparinized plasma, or serum.

!Note: Do not use separator tubes with a gel layer, as contact from the sample with the gel may falsely decrease PHB levels.[2]

Advantages of the VetScan Phenobarbital Profile

- Cost effective test that evaluates both PHB and liver values simultaneously.
- Immediately and thoroughly evaluate a patient receiving PHB medication when run with a complete blood count.
- Avoids the burden of waiting and high cost associated with send-out laboratory testing.
- Allows for immediate monitoring and titration of PHB for in-clinic client discussion and improved client compliance.

Conclusion

Once properly diagnosed and evaluated, control to minimize seizures can be accomplished with the use of anti-epileptic drugs. The VetScan Phenobarbital Profile provides proper clinical diagnostic monitoring of phenobarbital level so that it can be a safe and efficacious anti-seizure medication.

Appendix – Phenobarbital Drug Interactions

Listed below are more commonly used medications that may require higher doses in an animal on PHB due to microsomal p450 enzyme induction.[5] This list includes, but is not limited to the following medications:

- Corticosteroids
- Some antibiotics, including doxycycline
- Certain heart medications
- Metronidazole
- Mitotane
- Clomipramine
- Ketoconazole

Commonly used drugs inhibit microsomal enzymes and therefore may lead to increased PHB blood concentrations +/- hepatotoxicity.[2] This list includes, but is not limited to the following medications:

- Chloramphenicol
- Tetracycline
- Cimetidine and Ranitidine

Note: The p450 microsomal enzyme inducer is not reported in cats.[6]

PHB and Hypothyroidism[2]

Phenobarbital at therapeutic doses may decrease serum T4 and fT4 concentrations into a range consistent with hypothyroidism[2]. Increased TSH levels may be delayed. If there is concern for primary hypothyroidism, it is recommended to discontinue use of PHB to determine if the patient is truly hypothyroid, or if it is secondary to PHB usage. It may take up to 4 weeks after discontinuing PHB, for fT4 and T4 levels to return to normal.

Citations:

[1] Ettinger SJ, Feldman EC, Côté E. Textbook of Veterinary Internal Medicine: Diseases of the Dog and the Cat. 8th ed. St. Louis: Elsevier; 2017.

[2] Nelson RW, Couto CG. Small Animal Internal Medicine. 5th ed. St. Louis: Elsevier; 2013.

[3] Shell L. Maintenance Anticonvulsant or Antiepileptic Therapy - Pharmacology - Veterinary Manual. Merck Manual: Veterinary Manual. http://www.merckvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-nervous-system/maintenance-anticonvulsant-or-antiepileptic-therapy. Accessed April 28, 2017.

[4] Exact therapeutic ranges may differ depending on the manufacturer of laboratory equipment. Ranges specific to the Abaxis VetScan VS2 can be found in the package insert for the VetScan® Phenobarbital Profile rotor.

[5] Trepanier L. Top ten drug interactions in dogs and cats (Proceedings). dvm360.com. http://veterinarycalendar.dvm360.com/top-ten-drug-interactions-dogs-and-cats-proceedings?id=&sk=&date=&%0A%09%09%09&pageID=2. Published 2010. Accessed April 28, 2017.

[6] Truhaut R, Ferrando R, Graillot C, Gak JC, Fourlon C, Moraillon R. [Induction of cytochrome P 450 by phenobarbital in cats]. C R Acad Sci Hebd Seances Acad Sci D. 1978;286(4):371-373.