

TIMING OF BLOOD COLLECTION OF SERUM PHENOBARBITAL CONCENTRATIONS IN EPILEPTIC DOGS

Robin E. Levitski-Osgood, DVM, DipACVIM-Neurology

Epilepsy is an important problem in veterinary medicine. Most epileptic dogs benefit from administration of one or more anticonvulsant drugs. Sixty to eighty percent of epileptic dogs have improved seizure control with phenobarbital treatment alone.

Monitoring of serum phenobarbital concentrations is important in the management of epileptic dogs treated with this drug, because seizure control in dogs correlates best with serum phenobarbital concentration, not with the administered dose of phenobarbital. The therapeutic range for serum phenobarbital concentration in dogs has been established at 15 to 45 µg/ml, based originally on a study in which phenobarbital was documented to be an effective anticonvulsant in 60% of epileptic dogs when serum phenobarbital concentration was maintained in this range.

Present recommendations for epileptic dogs are to monitor trough (prior to next dose) and/or peak serum phenobarbital concentrations to evaluate whether drug concentrations are within the therapeutic range. Recommendations for the timing of peak serum phenobarbital concentrations vary from 2 to 4 hours up to 4 to 8 hours after administration of the medication. Coordination of such timing can be inconvenient for both the owner and clinician due to the difficulty in scheduling around a set dosing interval.

Phenobarbital has been reported to have a long elimination half-life in the range of 37 to 89 hours in normal dogs. This long elimination half-life makes it easy to maintain therapeutic serum concentrations throughout the day with minimal fluctuations between trough and peak serum drug concentrations when the drug is administered every 12 hours.

A retrospective study was performed to determine whether there were therapeutically relevant changes in serum phenobarbital concentrations throughout a daily dosing interval, and to determine whether careful timing of blood samples for serum phenobarbital concentrations was necessary.

Thirty-three client-owned epileptic dogs receiving phenobarbital on a q 12 hour dosing schedule for a minimum of three weeks were evaluated. Nine of these dogs were also receiving potassium bromide. No dog had received any known cytochrome P450-inducing or inhibiting drugs within three months prior to the study.

Serum phenobarbital concentrations were measured for each dog at 0, 3, and 6 hours after receiving phenobarbital orally. All serum phenobarbital concentrations were determined using a fluorescence polarization immunoassay validated for dog serum. For each dog, serum phenobarbital concentrations were evaluated to determine whether they were within the same therapeutic category (subtherapeutic <15 µg/ml, low-therapeutic 16-25 µg/ml, mid-therapeutic 26-35 µg/ml, high-therapeutic 36-45 µg/ml, and suprathereapeutic >45 µg/ml).

Dosages of phenobarbital ranged from 1.0 mg/kg/day to 10.9 mg/kg/day, with a mean of 5.8 mg/kg/day. The duration of phenobarbital treatment ranged from 3 weeks to 120 months, with a mean of 31 months and a median of 19 months.

Significant differences were not detected among mean serum phenobarbital concentrations when evaluated at 0, 3, and 6 hours for all dogs. Mean 0 hour, 3 hour, and 6 hour serum phenobarbital concentrations were 20.5 g/ml, 23 g/ml, and 22 g/ml, respectively.

Ninety-one percent (30/33) of dogs had 0, 3, and 6 hour serum phenobarbital concentrations in the same therapeutic category. Only 9% (3/33) of dogs had 0, 3, and 6 hour serum concentrations in different therapeutic categories with a >30% change in serum drug concentrations throughout the day.

There was a strong positive correlation between drug dosages and serum phenobarbital concentrations. The majority of dogs in this study had serum drug concentrations in the mid-therapeutic range or lower. None of the dogs with serum phenobarbital concentrations in the mid-therapeutic range or higher were receiving less than 6.0 mg/kg/day of phenobarbital with a median dose of 8.0 mg/kg/day.

Eighty percent of dogs in this study had an estimated phenobarbital elimination half-life between 20 and 140 hours. The mean and median estimated elimination half-lives were 65 and 50 hours respectively. On the basis of results from this study, most dogs receiving phenobarbital will reach steady state serum concentrations by 29 days (5.5 half-lives).

Results of this study suggest practical guidelines for monitoring serum phenobarbital concentrations. Serum phenobarbital concentrations can be measured at any time during the daily dosing interval in most epileptic dogs. Clinicians should monitor serum phenobarbital concentrations 3 to 4 weeks after initiating treatment or after a change in dose. The dosage of 6 to 8 mg/kg/day of phenobarbital can be used to treat dogs with newly diagnosed epilepsy, or to adjust dosages in poorly controlled epileptic dogs with subtherapeutic or low-therapeutic serum phenobarbital concentrations. Most of these dogs would be expected to have serum phenobarbital concentrations in the mid-therapeutic range (26 to 35 µg/ml) when evaluated 3 to 4 weeks after initiation of treatment.