Thyroid Function and Serum Hepatic Enzyme Activity in Dogs after Phenobarbital Administration

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Phenobarbital is the drug of choice for control of canine epilepsy. Phenobarbital induces hepatic enzyme activity, can be hepatotoxic, and decreases serum thyroxine (T₄) concentrations in some dogs. The duration of liver enzyme induction and T₄ concentration decreases after discontinuation of phenobarbital is unknown. The purpose of this study was to characterize the changes in serum total T₄ (TT₄), free T₄ (FT₄), thyroid-stimulating hormone (TSH), cholesterol and albumin concentrations, and activities in serum of alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) after discontinuation of long-term phenobarbital administration in normal dogs. Twelve normal dogs were administered phenobarbital at a dosage of approximately 4.4–6.6 mg/kg PO q12h for 27 weeks. Blood was collected for analysis before and after 27 weeks of phenobarbital administration and then weekly for 10 weeks after discontinuation of the drug. The dogs were clinically normal throughout the study period. Serum ALT and ALP activity and TSH and cholesterol concentrations were significantly higher than baseline at week 27. Serum T₄ and FT₄ were significantly lower. Serum albumin and GGT were not changed from baseline at week 27. Changes in estimate of thyroid function (TT₄, FT₄, TSH) persisted for 1–4 weeks after discontinuation of phenobarbital, whereas changes in hepatic enzyme activity (ALT, ALP) and cholesterol concentration resolved in 3–5 weeks. To avoid false positive results, it is recommended that thyroid testing be performed at least 4 weeks after discontinuation of phenobarbital administration. Elevated serum activity of hepatic enzymes 6–8 weeks after discontinuation of phenobarbital may indicate hepatic disease.

Keywords: Anticonvulsants; Epilepsy; Hepatotoxicity; Hypothyroidism; Seizures.

Epilepsy, including both inherited (idiopathic) and acquired forms, is a common neurologic disease of dogs. Phenobarbital, a barbiturate, is currently the drug of choice for control of canine epilepsy and other seizure disorders because of its low cost, efficacy, and minimal toxicity.

Potential adverse effects of phenobarbital administration include sedation, polyphagia, polyuria and polydipsia, and teratogenicity. One report of 3 dogs documented neutropenia and thrombocytopenia with long-term administration of phenobarbital. In addition, phenobarbital is hepatotoxic in some dogs. Phenobarbital is a potent inducer of cytochrome p450 and hepatic microsomal enzymes in dogs, with subsequent increases in serum activity of these enzymes making it difficult to detect hepatotoxicity. When enzyme induction resolves after withdrawal of phenobarbital is unknown, which confounds such determinations further.

In dogs, phenobarbital decreases total thyroxine (TT₄) and free T₄ (FT₄) concentrations and administration results in an increase in thyroid-stimulating hormone (TSH) concentration. Although the mechanism of these changes remains unproven in dogs, serum T₄ concentration is suspected to be decreased because of increased metabolism and excretion of the hormone secondary to hepatic microsomal enzyme induction, as is the case in humans and rodents. The length of time necessary for thyroid hormone concentrations to return to normal after discontinuation of long-term phenobarbital administration in the dog is unknown.

The purpose of this study was to characterize the changes in TT₄, FT₄, TSH and cholesterol concentrations, liver-related enzyme activities (alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]), and albumin after discontinuation of long-term phenobarbital administration (27 weeks) in normal dogs. This study represented a 2nd phase of a larger study examining the effects of long-term phenobarbital administration on liver, thyroid, and adrenal function testing.

Materials and Methods

Twelve adult neutered male dogs of various breeds, ranging from 11 to 23 kg in initial body weight and from 1 to 6 years in age, were housed in concrete outdoor kennels and were exercised once daily in a common grass lot. Breeds included 4 hounds, 2 medium-sized mixed breed dogs, and 6 Beagles. They received water and a commercial dry dog food ad libitum and were cared for according to the Guide for the Care and Use of Laboratory Animals of the National Research Council. Drugs or vaccines administered or chemicals used on every dog included yearly vaccinations against canine distemper, parvovirus, adenovirus 2, leptospirosis, coronavirus, parainfluenza virus, and rabies, with the last vaccination administered at least 5 months before the start of the study; monthly heartworm preventative; and daily disinfection of the concrete runs with a quarternary ammonia salt solution. All dogs were examined before phenobarbital initiation to determine general health status and to obtain basal values for the variables measured during the study. Each dog was used as its own control. Pre-treatment evaluation had included physical examination, a full chemistry panel 4 weeks before and immediately before phenobarbital initiation, complete blood count, and urinalysis. A Knott’s concentration
test for microfilaria and an enzyme-linked immunosorbent assay for antigen of adult heartworms were performed to rule out dirofilariasis. Feed was withdrawn at 5 PM on the days before all blood collections, providing a fasting time of at least 15 hours.

After collection of pretreatment values, a 27-week treatment course of phenobarbital was initiated at a dosage of 4.4–6.6 mg/kg PO q12h. Selected serum liver and thyroid variables were obtained after 5, 9, 17, 21, and 27 weeks of treatment. Phenobarbital was discontinued in all 12 dogs immediately before the beginning of this study. Serum was collected at week 27 and at weekly intervals thereafter for 10 weeks; thus, data for week 27 represented baseline for this study. Evaluation of liver enzyme activity in serum (ALP, ALT, GGT) and albumin, TT4, FT4, TSH, and cholesterol concentrations were performed at weeks 1–3, 5, 7, and 9 (ALP, ALT, GGT, albumin, and cholesterol); weeks 1–10 (TT4); weeks 1, 2, 4–6, 8, and 10 (FT4); and weeks 1, 2, 4–8, and 10 (TSH). Evaluation during and after phenobarbital administration included daily observations of activity and behavior and bi-weekly measurement of body weight and physical examination.

**Statistical Evaluation**

All data were considered continuous and evaluated for normality using the Shapiro–Wilk statistic. The data were considered to follow a normal distribution with failure to reject the null hypothesis of normality at P ≤ 0.05. All data were analyzed using the model

\[ y = \mu + \text{dog} + \text{week} + \text{dog-week} + e \]

where the effect of dog was considered random (therefore the interaction between dog and week was also random). A two-sided hypothesis with \( \alpha = 0.05 \) was used to determine the significance of week. Where week had a significant effect, comparisons of data from each week after discontinuation of phenobarbital were made to data from week 27 (baseline) using adjusted least-squares means with a Dunnet’s test maintaining an experiment-wise error of \( \alpha = 0.05 \). Thus, where a significant difference in the data from week 27 was noted, unless specified, the \( P \) value was <0.05. Proc mixed was used for the analysis. The data are summarized and graphed as mean ± SEM.

**Results**

Serum ALT, ALP, and cholesterol concentrations were significantly higher at week 27, whereas GGT and albumin remained unchanged from values before administration of phenobarbital. Serum ALP activity was significantly decreased from week 27 at weeks 1–9 after discontinuation of phenobarbital (Fig 1). Serum ALT activity was not significantly different from week 27 at weeks 1–3 after discontinuation of phenobarbital but was significantly decreased from week 27 at weeks 5–9 (Fig 1). Serum GGT activity was significantly increased above week 27 at weeks 1–7 after discontinuation of phenobarbital but was not significantly different from week 27 at week 9 (Fig 1). Serum albumin concentration was not significantly different from week 27 at weeks 1 and 3 after discontinuation of phenobarbital but was significantly increased from week 27 at weeks 2, 5, 7, and 9 (Fig 2). Serum cholesterol was significantly decreased from week 27 at weeks 2, 3, 5, 7, and 9 after discontinuation of phenobarbital (Fig 2).

**Serum Thyroid Parameters**

TT4 and FT4 were significantly decreased, whereas TSH concentration was significantly increased at week 27 from values before phenobarbital administration. Serum TT4 concentration was not significantly different from week 27 at week 3 after discontinuation of phenobarbital but was significantly increased from week 27 at weeks 1, 2, and 4–10 (Fig 3). Serum FT4 concentration was not significantly different from week 27 at weeks 1, 2, 4, and 10 after discontinuation of phenobarbital but was significantly increased from week 27 at weeks 5, 6, and 8 (Fig 3). Serum TSH concentration was not significantly different from week 27 at anytime after discontinuation of phenobarbital (Fig 3).

**Discussion**

In dogs with epilepsy or other seizure disorders, lifelong treatment with phenobarbital is often required. However, occasions occur where the drug may be withdrawn. Potential reasons include lack of seizure activity for an extended period, the desire to switch to a potentially less toxic anticonvulsant such as potassium bromide, or toxicity related to phenobarbital administration.13
Hepatotoxicosis is a limiting factor to the use of phenobarbital as an anticonvulsant in some dogs.1,3,6,7,17–19 However, determining if increases in serum activity of liver specific enzymes in a dog presenting for nonspecific clinical signs are due to hepatotoxicosis or because of a drug-induced enzyme induction can be difficult. When hepatotoxicosis is suspected, it is recommended that phenobarbital be discontinued and that the anticonvulsant treatment regimen be changed if possible.

Although serum ALP and ALT are increased by phenobarbital administration, AST and total bilirubin and bile acid concentrations are not and therefore are potential indicators of hepatotoxicosis.3,8,12 In a retrospective study of 18 dogs with hepatotoxicosis secondary to phenobarbital administration, hypalbuminemia occurred in 75%, and elevations in ALP, ALT, bile acids, and total bilirubin were documented in 100, 85, 33, and 40%, respectively.14 The average duration of treatment was 39 months, and 75% of dogs had a serum phenobarbital concentration of greater than 40 µg/mL. Examination of liver biopsies of 3 dogs revealed hepatic fibrosis and nodular regeneration. Reduction of the phenobarbital dose or discontinuation of the drug resulted in clinical improvement in 60% of dogs. Serum phenobarbital concentrations did not decrease for several days, but the changes in hepatic enzyme activity in serum after phenobarbital reduction or discontinuation were not reported.18

The present study has clinical relevance in that activity of hepatic enzymes in serum that is still significantly abnormal at least 6 weeks after discontinuation of phenobarbital should lead the clinician to reevaluate the dog for hepatotoxicosis or other liver disease. In the dogs of this study, changes in serum activity of hepatic enzymes (ALT, ALP, GGT) and cholesterol concentration resolved 1–5 weeks after discontinuation of the drug. Based on these findings, it can be recommended that serum ALP, ALT, GGT, and cholesterol be reevaluated at least 6 weeks after discontinuing drug therapy.

In dogs, ALP can be elevated secondary to cholestasis, osteolysis, endogenous or exogenous corticosteroids, or drug-induced enzyme induction.20 In the dogs of this report, no histologic evidence of cholestasis was found. Therefore, the ALP elevations likely were attributable to phenobarbital-induced enzyme changes.12 In dogs treated with glucocorticoids, the ALP can remain elevated for weeks to months despite discontinuation of the drug.20,21 ALP increases had declined to within the reference range after 3 weeks, and had resolved within 5 weeks in the dogs reported here. Phenobarbital-induced ALP changes possibly resolved quickly because phenobarbital levels would rapidly decline after discontinuation (along with its enzyme-inducing properties), whereas effects of glucocorticoids persist after the drug has been eliminated.21

Serum ALP is increased secondary to hepatocellular damage or drug-induced enzyme induction.22 Serum AST is often concurrently elevated when hepatocellular injury is
but a less sensitive indicator of liver disease than is ALP.\textsuperscript{23} Previous studies demonstrated a decrease in serum albumin after long-term phenobarbital administration in dogs.\textsuperscript{8} Although the dogs in this report did not have significantly decreased serum albumin after 27 weeks of drug administration, a significant increase occurred at weeks 2, 5, 7, and 9 after discontinuation of phenobarbital. This finding could support the idea that phenobarbital induces a defect in albumin synthesis, with a rebound effect resulting in an increase in albumin after the drug is discontinued. Also, this increase in albumin could represent subclinical dehydration because the dogs’ water consumption possibly decreased after discontinuation of the drug.

Detection of hypothyroidism in dogs receiving phenobarbital can be difficult, because signs such as weight gain and lethargy are common findings in both hypothyroid dogs and in dogs receiving phenobarbital.\textsuperscript{1,2,24} In addition, hypercholesterolemia is common in hypothyroidism and has been reported after phenobarbital administration.\textsuperscript{1,24} The mechanism of T4 decreases in dogs receiving phenobarbital remains unproven. Phenobarbital-induced hepatic enzyme induction may result in increased clearance of triiodothyronine (T₃) and T₄ by the liver, as is the case in rodents.\textsuperscript{13} Increased conversion of T₄ to T₃ in peripheral tissues may also play a role.\textsuperscript{10,11} Subsequent to decreased peripheral T₃ concentrations, TSH concentration may be increased as a result of loss of feedback.\textsuperscript{24}

In the dogs of this report, thyroid hormone changes resolved in 1 (TT₄) to 5 (FT₄) weeks after phenobarbital was discontinued. Mild elevations in TSH concentrations that occurred during phenobarbital administration resolved immediately after discontinuation of the drug at week 27.\textsuperscript{12} A lack of TSH increase upon phenobarbital withdrawal supports the theory that hypothalamic–pituitary–thyroid gland axis suppression plays a minimal role in TT₄ and FT₄ depression during phenobarbital administration. Therefore, other mechanisms such as increased metabolism of thyroid hormone by the liver may be more likely. Perhaps if TSH concentrations are increased during the withdrawal period, a diagnosis of primary hypothyroidism should be considered. However, careful and repeated evaluation of the patient’s thyroid status is recommended to confirm a diagnosis of hypothyroidism because FT₄ concentrations could still be depressed by 10 weeks after withdrawal (see Fig 3).

Further studies that follow dogs for a longer time period are needed to determine exactly how long thyroid hormone changes persist after phenobarbital is withdrawn. Further studies might also evaluate the measurement of TT₄ and FT₄ 6 hours post-TSH injection in normal dogs before, during, and after chronic phenobarbital therapy for its usefulness in accurately measuring thyroid function in dogs during phenobarbital therapy. Based on the findings of this study, it is recommended that thyroid values be evaluated at least 6 weeks after cessation of phenobarbital.

The dogs of this report had no significant changes in GGT at 27 weeks of phenobarbital administration, although significant increases were reported at weeks 13–21.\textsuperscript{12} This supports the theory that GGT is less influenced by enzyme-inducing drugs than is ALP. Although reasons for a significant increase in GGT after discontinuation of phenobarbital are unknown, it should be noted that none of the GGT values were above reference ranges during that time.

In the dogs of this study, neither cytologic evidence of hepatocellular damage nor AST elevation occurred, supporting the idea that the ALT elevation was induced secondary to phenobarbital.\textsuperscript{15} The half-life of serum ALT is approximately 1–2 days, and ALT is expected to decrease over 1–2 weeks after hepatic damage ceases.\textsuperscript{22} In a study of 6 dogs with hepatopathy induced by glucocorticoid administration, ALT elevations persisted for 6 weeks after discontinuation of the steroids.\textsuperscript{21} This is comparable to the 5 weeks that it took for the dogs of this report to return to pretreatment values. Although reasons for this persistent elevation are unknown, it should be noted that none of the ALT values were above reference ranges after discontinuation of phenobarbital.

GGT can be elevated secondary to drug-induced hepatic enzyme induction or cholestasis.\textsuperscript{20,21} GGT is more specific but a less sensitive indicator of liver disease than is ALP.\textsuperscript{23}

Fig 3. Mean ± SEM serum total thyroxine (TT₄), free T₄ (FT₄), and thyroid-stimulating hormone (TSH) concentrations. Dotted line on TT₄ graph represents upper reference concentrations for normal range, suspect range, and low reference range concentrations. Dotted line on TSH concentration may be increased as a result of loss of feedback.\textsuperscript{24} See Figure 1 for legend.
In summary, the findings of our study support the idea that changes in liver enzymes, albumin, cholesterol, and thyroid parameters induced by phenobarbital in normal dogs treated for 27 weeks resolve 1–5 weeks after cessation of therapy. These data may be of aid to practitioners in the evaluation of dogs with suspected hepatotoxicosis secondary to phenobarbital administration, of dogs on phenobarbital suspected of having hypothyroidism, and in the general screening of dogs from which phenobarbital has been withdrawn.

Footnotes

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