Short term influence of prednisone and phenobarbital on thyroid function in euthyroid dogs

Sylvie Daminet, Manon Paradis, Kent R. Refsal, Christopher Price

Abstract — The short term effects of prednisone and phenobarbital on serum total thyroxine (tT4), free thyroxine (fT4), and thyroid stimulating hormone (TSH) were evaluated in euthyroid dogs. Twenty-six beagles were randomly divided into 3 groups receiving, respectively, a placebo, prednisone (1.2 to 2 mg/kg body weight, per os, every 12 hours for 3 weeks), or phenobarbital (1.8 to 3 mg/kg body weight for 1 week, then 2.7 to 4.5 mg/kg body weight, per os, every 12 hours for 2 weeks). Blood samples taken over a 6-week period were assayed for serum tT4, fT4, and TSH. Phenobarbital therapy in our study did not affect serum tT4, fT4, or TSH concentrations. Prednisone therapy, however, significantly decreased serum tT4 and fT4, but did not affect serum TSH concentrations.

Résumé — Influence à court terme de la prednisone et du phénobarbital sur la fonction thyroïdienne de chiens euthyroïdiens. L'effet à court terme de la prednisone et du phénobarbital sur la thyroxine sérique totale (T4t) la thyroxine libre (T4l) et la thyrotrophine (TSH) ont été mesurées chez des chiens euthyroïdiens. Vingt-six Beagles ont été divisés au hasard en 3 groupes et ont respectivement reçus un placebo, de la prednisone (1,2 à 2 mg/kg de poids corporel, per os, aux 12 h, pendant 3 semaines) ou du phénobarbital (1,8 à 3 mg/kg de poids corporel, pendant 1 semaine puis 2,7 à 4,5 mg/kg de poids corporel, per os, aux 12 h, pendant 2 semaines). Des échantillons de sang pris sur une période de 6 semaines ont été analysés afin de déterminer la T4t sérique, la T4l et la TSH. Dans notre étude, le traitement au phénobarbital n'a pas affecté les concentrations de T4t sérique, de T4l ou de TSH. Le traitement à la prednisone a cependant diminué de façon significative la T4t sérique et la T4l mais n'a pas modifié les concentrations sériques de TSH.

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Introduction

The measurement of serum concentrations of total thyroxine (tT4) is frequently used to assess thyroid function in dogs. Serum tT4 concentrations are influenced by many factors, including daily fluctuations, severe nonthyroidal diseases, obesity, and certain drugs (1–3). Because of these influences, the measurement of a basal tT4 concentration is frequently unreliable as an indicator of thyroid function in dogs. Theoretically, free thyroxine (fT4) concentrations should be less subject to these variations (4). The most reliable assay for fT4 is by equilibrium dialysis, which is becoming more readily available from diagnostic laboratories (5). Until recently, the easiest and most reliable test to evaluate canine thyroid function was the thyroid-stimulating hormone (TSH) stimulation test. However, the bovine TSH used to perform this test is no longer commercially available. Recently, methods to evaluate canine endogenous TSH have become available and seem promising for accurate assessment of canine thyroid function (6–9).

Several drugs have been shown to alter thyroid function in humans, rats, and dogs (2,10). Drugs frequently used in canine practice and known to alter thyroid function in man and rats include glucocorticoids and phenobarbital. Studies performed with humans and rats have demonstrated that endogenous or exogenous glucocorticoids directly inhibit the hypothalamic-pituitary-thyroid axis and also influence peripheral metabolism of thyroid hormones (11–14). Although several studies in dogs have reported the effects of exogenous or endogenous glucocorticoids on tT4, fT4, and triiodothyronine (T3), their effects on endogenous TSH are unknown (15–19).

In rats, phenobarbital alters thyroid function by affecting the peripheral elimination of T4 (10,20). Indeed, increased hepatic deiodination of thyroid hormones, increased biliary clearance, and increased fecal excretion result in decreased concentrations of circulating thyroid hormone, which, in turn, increase TSH secretion through the classical negative feedback pathway (20–22). Phenobarbital could also have additionnal central effects on the hypothalamus-pituitary-thyroid axis (23,24). Most studies in rats report decreased T4 with normal or, more often, increased TSH concentrations (21,23,25). In humans, phenobarbital increases the metabolic clearance of T4 through increased deiodination and biliary

Département de sciences cliniques (Daminet, Paradis), Département de biomédecine vétérinaire (Price), Faculté de médecine vétérinaire, Université de Montréal, C.P. 5000, Saint-Hyacinthe (Québec) J2S 7C6. Animal Health Diagnostic Laboratory (Refsal), Michigan State University, East Lansing, Michigan 48824 USA.

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clearance of thyroid hormones, as well as by an enhanced hepatocellular binding (26,27). In veterinary medicine, phenobarbital is often listed as a drug that can potentially decrease canine tT4 levels (1,2), but to our knowledge, there are no published studies available on the effects of phenobarbital on thyroid function in dogs.

The objective of this study was to evaluate the influence of short term oral prednisone and phenobarbital on canine thyroid function.

Materials and methods

Dogs

Twenty-six sexually intact, adult beagles (11 females, 15 males; 2 to 3 y old) were assessed as healthy based on results of physical examination, complete blood cell count and biochemical profile, and normal serum tT4, fT4, and TSH concentrations. The dogs were randomly divided into 3 groups. Group 1 consisted of 8 dogs, 3 females and 5 males. Group 2 contained 9 dogs, 4 females and 5 males. Group 3 consisted of 9 dogs, 4 females and 5 males. The mean body weights of these dogs were 11.07 kg ± 0.59, 11.4 ± 0.76, and 10.7 ± 0.7 for Groups 1, 2, and 3, respectively. All dogs were housed indoors, in 6 runs containing 4 to 5 dogs each. A one-week acclimation period was allowed before starting the experiment. Environmental conditions, such as photoperiod (12 h on, 12 h off), ventilation, temperature, and humidity were kept constant throughout the study. The dogs were fed a standard commercial maintenance pellet diet twice daily and water was available ad libitum.

Experimental protocol

Dogs in Group 1 received a placebo (Lactose, Odan Ltée Laboratories, Montreal, Quebec) for 3 wk. Dogs in Group 2 were given prednisone (Apotex, Weston, Ontario) at a dosage ranging from 1.2 to 2 mg/kg body weight (BW), PO, q12h for 3 wk. Dogs in Group 3 were given phenobarbital (Parke-Davis, Scarborough, Ontario) at a dosage ranging from 1.8 to 3 mg/kg BW, PO, q12h for the first week, then from 2.7 to 4.5 mg/kg BW for the next 2 wk. Monitoring was continued for 6 wk, with the treatments administered during the first 3 wk of the study.

Blood samples (18 mL) were taken by jugular venipuncture before initiating therapy (T0), at 48 h, and after 1, 3, 4, 5, and 6 wk. All blood samples were taken between 0800 and 0900. Blood samples were immediately centrifuged and serum was frozen in 4 aliquots at −20°C, until assayed.

The protocol was approved by the Ethics Committee of the Faculté de médecine vétérinaire of the University of Montreal, and procedures were performed in accordance with the recommendations of the Canadian Council on Animal Care.

Assays for tT4, fT4 and TSH

Assays for tT4, fT4, and TSH were performed on all samples. Total thyroxine concentrations were determined by using a commercially available solid-phase radioimmunoassay (Coat-A-Count canine T4, Diagnostic Products, Los Angeles, California, USA) previously validated for canine serum (15). Assays for fT4 concentrations by equilibrium dialysis were performed by using a commercial assay kit (Free T4 by equilibrium dialysis Nichols Institute Diagnostics, San Juan Capistrano, California, USA) at the Endocrine Section, Animal Health Diagnostic Laboratory, Michigan State University. Assay procedures were performed as per the manufacturer's instructions. The manufacturer of the kit reported negligible crossreactivity of other iodothyronines (range of 0.044% to 0.001%) in the assay. For estimates of assay repeatability, 3 pools of canine serum were established. In canine serum with a mean concentration of 15, 37, or 96 pmol/L, the interassay coefficient of variation (CV) was 18.6%, 14.2%, and 6.9%, respectively (n = 10 assays). In the same serum pools, intraassay CV was 14.5%, 10.2%, and 6.6%, respectively (10 replicates). Canine serum with a concentration of fT4 of 111 pmol/L was diluted with "0" standard prior to placement in the dialysis chamber. In serum diluted with standard at rates of 1:1, 1:2, or 1:4, 100%, 74%, and 70% of expected concentrations of fT4 were measured in the assay. Thyroxine was added in varying amounts to aliquots of dialysate harvested after prior incubation with canine serum. The concentration of fT4 in the dialysate was 11 pmol/L after incubation with serum and before addition of exogenous T4. When T4 was added to dialysate at concentrations of 13, 26, 52, or 77 pmol/L, 92%, 95%, 99%, and 92% of added T4, respectively, was measured in the assay. The sensitivity of the assay, defined as the concentration of fT4 at the point of 90% of total specific binding, was 1.8 pmol/L (mean of 10 assays). Serum TSH concentrations were determined by using a commercially available solid-phase radioimmunoassay (Coat-A-Count canine TSH IRMA, Diagnostic Products) recently validated in the dog (7,9). The intraassay CV was 7% for samples with a TSH concentration below 1 ng/mL, and 0.8% for samples with a TSH concentration above 1 ng/mL. The interassay CV was 7% for samples with a mean TSH concentration of 3 ng/mL, and 26% for samples with a mean TSH concentration of 0.11 ng/mL. Dilutional parallelism, evaluated through assaying serum at 4 dilutions, was respected. The limit of detection was 0.03 ng/mL.

Serum phenobarbital concentrations

Serum concentrations of phenobarbital were determined for dogs in Group 2, in samples from weeks 1 and 3, by using an enzymatic technique (Cedia Phenobarbital, Boehringer Mannheim, Indianapolis, Indiana, USA) at a commercial laboratory (Vita-Tech, Ontario).

Data analysis

Data were analyzed by 2-way analysis of variance for repeated measures. When there were significant time-by-treatment interactions, a Dunnett's procedure was used to compare the groups at each time period. Data are presented as mean ± standard error of the mean ($s_{\bar{x}}$). Results were considered significant at $P < 0.05$.

Results

Total thyroxine concentrations

There was a significant effect of time on tT4 concentrations in the control and the prednisone groups (Figure 1, $P < 0.05$). There was a significant interaction between time and group; therefore, differences between

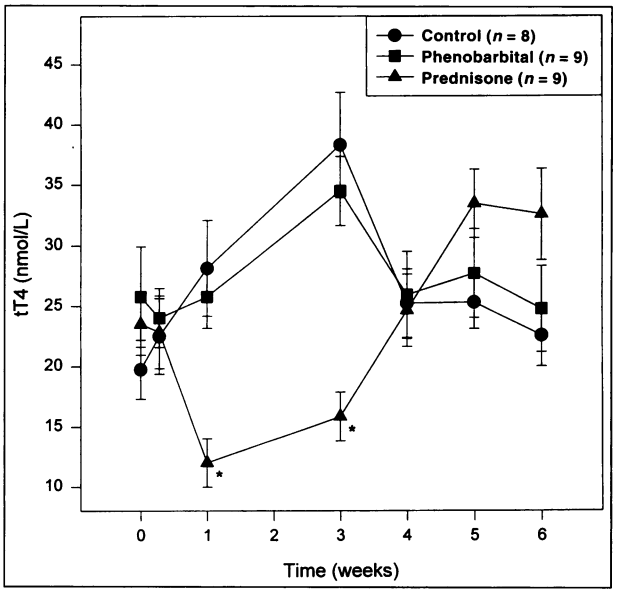

Figure 1. Mean (± $s_{\bar{x}}$) tT4 concentrations in beagles during and after placebo, prednisone (1.2 to 2 mg/kg BW, PO q12h) or phenobarbital (1.8 to 3 mg/kg BW for 1 wk, then 2.7 to 4.5 mg/kg BW PO, q12h) administration. Medications were administered during the first 3 wk of the experiment. *Significantly different from control group ($P < 0.05$).

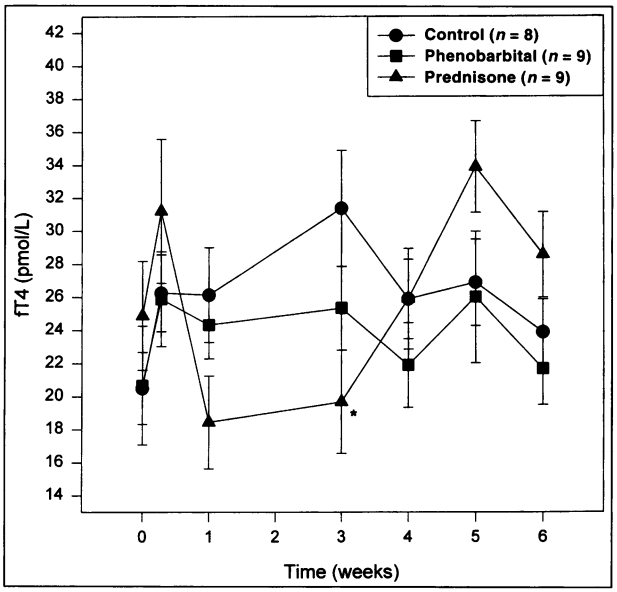

Figure 2-Mean (± $s_{\bar{x}}$) fT4 concentrations in beagles during and after placebo, prednisone (1.2 to 2 mg/kg BW PO, q12h) or phenobarbital (1.8 to 3 mg/kg BW for 1 wk, then 2.7 to 4.5 mg/kg BW PO, q12h) administration. Medications were administered during the first 3 wk of the experiment. *Significantly different from control group ($P < 0.05$).

groups were analyzed at each time period. After 1 and 3 wk of treatment, tT4 concentrations were significantly lower in the prednisone group compared with the control group (week 1; 12 ± 2 nmol/L and 28.1 ± 4 nmol/L, respectively; week 3; 15.8 ± 2 nmol/L and 38.3 ± 4.4, respectively). Phenobarbital therapy did not significantly affect tT4 values at any time (Figure 1).

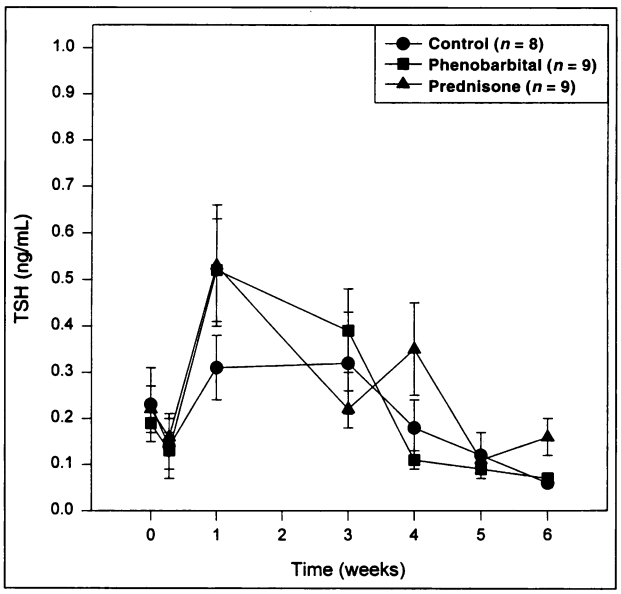

Figure 3-Mean (± $s_{\bar{x}}$) TSH concentrations in beagle dogs during and after placebo, prednisone (1.2 to 2 mg/kg BW PO, q12h) or phenobarbital (1.8 to 3 mg/kg BW for 1 wk, then 2.7 to 4.5 mg/kg BW PO, q12h) administration. Medications were administered during the first 3 wk of the experiment ($P < 0.05$).

Free thyroxine concentrations

There was a significant effect of time on fT4 concentrations in the control and the prednisone groups (Figure 2, $P < 0.05$), and a significant interaction between time and group. A significant decrease in fT4 concentrations was found at 3 wk in the prednisone group when compared with the control group (19.7 ± 3.1 pmol/L and 31.4 ± 3.5 pmol/L, respectively). Phenobarbital did not significantly affect the fT4 concentrations at any time (Figure 2).

Serum TSH concentrations

There was a significant effect of time on TSH concentrations in all 3 groups (Figure 3, $P < 0.05$). There was neither significant effect of group, nor an interaction between time and group. All concentrations for TSH levels were within the normal reference range throughout the study (< 0.7 ng/mL).

Serum phenobarbital concentrations

Measurement of serum phenobarbital concentrations after 1 wk of therapy revealed that the recommended therapeutic level of phenobarbital (65 to 150 µmol/L) had been obtained in 6 out of 9 dogs (28). Most dogs had serum concentrations towards the lower end of the therapeutic range (71.4 ± 4.4 µmol/L). After the dosage of phenobarbital had been increased by 50% in all dogs for the next 2 wk, the serum phenobarbital concentrations were again at the lower end of the therapeutic range (67.4 ± 5.6 µmol/L). There was no correlation between serum phenobarbital levels and serum concentrations of tT4, fT4, or TSH. Side effects from phenobarbital administration, such as ataxia or lethargy, were not noticed.

Discussion

The effects of prednisone on canine endogenous TSH and the effects of phenobarbital on thyroid function in dogs are unknown. Our finding that prednisone given at an immunosuppressive dosage significantly suppressed tT4 at 1 and 3 wk and fT4 levels after 3 wk of therapy is in agreement with a previous study by Torres et al (15) but contrasts with that by Moore et al (18). Torres et al reported a decrease in canine tT4 and fT4 levels at 24 h and 3 wk after initiating oral prednisone therapy at an immunosuppressive dosage. However, serum thyrotropin concentrations were not determined and fT4 concentrations were not assayed by equilibrium dialysis, which is now considered the most reliable technique to determine fT4 levels (5,29,30). Moore et al later reported that 1 mo of oral prednisone did not affect basal tT4 levels in normal dogs, but a lower antiinflammatory dose of prednisone was used. The effects of glucocorticoids have previously been documented to be dependent on the dosage, route of administration, duration of treatment, and chemical form used (15,31).

The fact that, in our study, serum TSH concentrations were not significantly affected by prednisone administered orally at an immunosuppressive dosage during a 3-week period, suggests that the measurement of TSH concentrations in euthyroid dogs receiving short-term prednisone therapy may be a more reliable tool than that of tT4 to evaluate thyroid function. However, this is in contrast to studies in humans, in which TSH concentrations were decreased by exogenous or endogenous glucocorticoids (11,12,32–35). It is possible that a suppression of TSH secretion is less easily detected in dogs compared with humans, because euthyroid dogs have TSH concentrations very close to the limit of detection of the current assay. It is also possible that there is a species difference between dogs and humans in the pituitary response to glucocorticoids. In the clinic, TSH measurement is frequently used in combination with tT4 or fT4 to evaluate thyroid function in dogs (8). Further studies to assess the effects of glucocorticoids on hypothyroid dogs with high TSH levels are needed.

The mechanism of action of glucocorticoids on thyroid function appears complex, with suppression of TSH release reported in humans (12–14,32,36–38) and rats (37,38), and disturbed T3 and T4 partition, clearance rates, and metabolism reported in humans (13,39), rats, and dogs (15–17,31). Our study was not designed to determine the mechanism of action of glucocorticoids on thyroid function.

Another commonly used drug that may affect thyroid function is phenobarbital. In rats, phenobarbital increases biliary thyroid hormone excretion, which decreases serum tT4 levels with normal or, more often, increased TSH levels (20–25,40). There are no published studies on the effects of phenobarbital on thyroid function in dogs, but, by extrapolation, phenobarbital is often listed as a drug that can potentially affect canine thyroid function (1,2). Recently, 2 short communications have suggested that long-term administration of phenobarbital influences canine thyroid function (41,42). Surprisingly, in our study, phenobarbital did not significantly affect tT4, fT4, or TSH concentrations. Interestingly, most studies in rats report decreased levels of tT4 and increased levels of TSH, but the dosages administered to these rats were extremely high (100 mg/kg BW/d) and serum levels of phenobarbital were not determined (20,23,25). Hepatic enzyme induction and decreased concentrations of tT4 in rats receiving phenobarbital are dose-related (24). Most studies in humans report no significant changes of tT4 and TSH levels in epileptic patients taking phenobarbital (10,26,27,43). Dosages of phenobarbital administered to human patients range from 1 to 5 mg/kg BW/d, a dose similar to the recommended initial dosage for phenobarbital in dogs.

In the present study, serum phenobarbital concentrations after 1 wk of treatment were at the lower end of the therapeutic range in Group 2 dogs. As the elimination half-life of phenobarbital in beagles is much shorter than in other breeds, serum steady-state concentrations should be achieved after 1 wk, instead of 2 to 3 wk (44–46). To reach higher therapeutic concentrations, the initial dosage of phenobarbital was increased by 50% in all dogs of Group 2 for the next 2 wk. Despite these higher doses of phenobarbital, serum concentrations of phenobarbital were somewhat lower than expected. This suggest that short-term administration of phenobarbital, at antiepileptic dosages, does not affect thyroid function in dogs.

There was a significant effect of time on tT4, fT4, and TSH concentrations in the control group. Several factors can influence basal tT4 and, less severely, fT4 concentrations in dogs (3). Factors such as photoperiod, humidity, ambient temperature, and body weight were constant throughout the experiment, making it unlikely that they were responsible for the variation of the hormone concentrations in the control group. Also, the dogs were allowed to acclimatize for a period of 1 wk. It has been reported that, in females, increased progesterone levels can increase tT4 levels (47), although another study suggests no difference in tT4 concentrations between male and female dogs (48). The females in our study were in anestrus, based on the absence of clinical signs compatible with proestrus and estrus throughout the study. Furthermore, the tendency toward increased concentrations of tT4 after 1 and 3 wk of treatment was noted in both the female and male dogs of the control group.

In conclusion, oral prednisone administered over a 3-week period at immunosuppressive dosages significantly suppressed tT4 and fT4 concentrations, but did not affect TSH concentrations. Short-term administration of phenobarbital does not significantly alter canine thyroid function.

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