Effects of Anti-Inflammatory and Immunosuppressive doses of Prednisolone on Serum Triiodothyronine, Thyroxine, and free Thyroxine Concentrations and Thyroid Morphology in the Dog.

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SUMMARY

The aim of the present study was to determine the effects of different oral doses of prednisolone (classically used during anti-inflammatory and immunosuppressive therapies with decreasing and/or alternate day protocol scheme) on the serum triiodothyronine (T₃), thyroxine (T₄) and free T₄ (fT₄) concentrations and thyroid gland morphology. Prednisolone was given orally at gradually decreased doses, from 1.1 mg / kg / day to 1.1 mg / kg / alternate day for 21 days in group I (n = 8) and from 2.2 mg / kg / day to 0.25 mg / kg / day for 50 days in group II (n = 7). Serum samples were obtained from treated mixed breed dogs before treatment, after each dose reduction and 15 days after the end of treatment. Seven dogs (group III) served as controls. Thyroid biopsies were surgically obtained on days 22 and 37 in group I, on days 51 and 66 in group II and on days 22 and 51 in group III.

With prednisolone high doses, early decreases of serum T₃ and fT₄ concentrations (p < 0.05) were obtained in group I (on day 8) and in group II (on day 11). The alteration of thyroid function has persisted until the 21st day with low T₃, T₄ and fT₄ concentrations in group II. As soon as doses were markedly reduced, hormone concentrations significantly increased for reaching even overtaking pre-treatment values fifteen days after the end of treatments. Light and electron microscopic examinations revealed that inactive follicle areas were seen among the active follicle areas in both treatment groups, especially in group II. Despite the increase in the number of the colloid droplets, less or no lysosomes were seen in follicle epithelial cells in treated groups. Thyroid glands recovered normal appearance within 15 days post-treatment.

In conclusion, gradually decreased and/or alternated doses of prednisolone, used in anti-inflammatory and immunosuppressive therapies caused transient changes not only in serum T₃, T₄ and fT₄ concentrations, but also in thyroid morphology (although changes were more prolonged) and allowed relevant adaptative mechanisms to occur.


Introduction

Prednisolone, a well-known drug, has been used for its anti-inflammatory and immunosuppressive effects for the treatment of various diseases [17]. In order to avoid the adverse effects, such as suppression of the hypothalamo-hypophyseal-adrenocortical axis, doses should be tapered over several days [11]. BEHREND and KEMPRAINEN [1] have given schedules, one tapering for immunosuppressive effect and one for progression from twice daily to once daily and then every other day for anti-inflammatory protocol. They have also described these 2 alternatives; giving the same dose every day or doubling the dose every other day (in order to maintain constant the total dose).

Prednisolone causes remarkable decreases on triiodothyronine (T₃), thyroxine (T₄) and free T₄ (fT₄) concentrations affecting various stages of hypothalamo-hypophyseal-thyroid axis, and T₃ - T₄ transport capacity of serum globulins in animals and human beings [3, 12, 13, 16, 20]. In addition, structures, doses and administration route, treatment duration of corticoids may all interfere with thyroid function and

RéSUMÉ

Effets de la prednisolone à doses anti-inflammatoires et immunosuppressives sur les concentrations sériques de Triiodothyronine, Thyroxine, et Thyroxine libre et sur la morphologie de la thyroïde chez le chien. Par A. KURTDEDE, R.N. ASTI, T. SEL, N. KURTDEDE, H. KARAGUL, O. ATALAY et M. GUZEL.

L’objectif de cette étude est de déterminer les effets de la prednisolone administrée par voie orale à doses fractionnées et/ou alternées classiquement utilisées dans les traitements anti-inflammatoires et immunosuppressifs sur les concentrations de T₃, T₄ et de T₄ libre ainsi que sur la morphologie de la thyroïde chez le chien.

Dans le groupe I (n = 8), les doses orales de prednisolone ont progressivement été diminuées pendant 21 jours allant de 1.1 mg / kg / jour à 1.1 mg / kg / jour alterné, et dans le groupe II (n = 7), les doses employées ont été de 2.2 mg / kg / jour à 0.25 mg / kg / jour pendant 50 jours. Les sérum des chiens de races variées ont été recueillis avant traitement, à chaque réduction des doses et 15 jours après l’arrêt des traitements. Sept chiens (groupe III) ont servi de contrôles. Les biopsies de la thyroïde ont été réalisées chirurgicalement à J22 et J37 pour le groupe I, à J51 et J66 pour le groupe II et à J22 et J51 pour le groupe III.

Avec de fortes doses de prednisolone, les concentrations de T₃ et de T₄ libre ont diminué précocement (p < 0.05) dans le groupe I (J8) et dans le groupe II (J11), et l’altération de la fonction thyroïdienne caractérisée par des concentrations faibles en T₃, T₄ et T₄ libre a persisté jusqu’à J21 dans le groupe II. Dès que les doses ont été nettement réduites, les concentrations hormonales ont significativement remonté jusqu’à atteindre, voire dépasser les concentrations initiales 15 jours après l’arrêt des traitements. Les examens en microscopie optique et électronique ont révélé la présence, dans les 2 groupes traités et plus particulièrement dans le groupe II, de follicules inactifs parmi les structures fonctionnelles. Malgré le grand nombre de vésicules de colloid droplets observées dans les cellules éphéliales folliculaires, peu ou pas de lysosomes ont été mis en évidence. La thyroïde a retrouvé un aspect normal dans les 15 jours suivant l’arrêt des traitements.

En conclusion, les doses progressivement décroissantes et/ou distribuées à jour alterné de prednisolone lors de traitements anti-inflammatoires et immunosuppressifs causent non seulement des modifications transitoires des concentrations hormonales (T₃, T₄ et T₄ libre) mais aussi de la morphologie de la thyroïde de façon plus prolongée et permettent la mise en place de mécanismes adaptatifs et efficaces.

induce changes in T₃, T₄ and fT₄ concentrations [1, 20, 24]. However, thyroid function can improve within 2 weeks after termination of treatment [16, 18].

After prednisolone administration, the numbers of colloidal droplets in thyroid follicular cells have increased, and T₃ and T₄ concentrations decreased. These modifications may be due to the inhibition of lysosomal hydrolysis of colloids by prednisolone [13, 23, 24].

Although the effects of various doses of prednisolone on serum T₃, T₄ and fT₄ concentrations and thyroid morphology have been previously reported [6, 10, 12, 16, 19, 23], the consequences on thyroid function of prednisolone doses clinically used during anti-inflammatory and immunosuppressive treatments were not explored.

The aims of the present study were to determine the effects of different doses of prednisolone (used in anti-inflammatory and immunosuppressive therapies using tapering and/or alternate day protocol scheme) on the serum T₃, T₄ and fT₄ concentrations and morphology of thyroid gland.

Materials and Methods

A) ANIMALS

Twenty-two mixed breed dogs aged 2-4 years and weighing 12-30 kg were included in the present study. All dogs were checked for their health status and were detected to be euthyroid based on the normal range of serum T₃, T₄ and fT₄ concentrations before the prednisolone administration. Dogs were kept under observation for 21 days prior to the study. Dogs were randomly divided into three groups. Group I (Anti-inflammatory group) consisted of 8 dogs weighing 23 kg in average (15 kg - 30 kg). Group II (Immunosuppressive group) consisted of 7 dogs weighing 22 kg in average (12 kg - 30 kg). Group III (Control group) consisted of 7 weighing 20 kg in average (12 kg - 30 kg).

In group I, anti-inflammatory doses of prednisolone (Prednol tab® 16 mg/tablet methylprednisolone, Mustafa Nevzat, Turkey) were administered orally at a dose of 0.55 mg/kg twice a day (at 9 am and 9 pm) for the first week, 0.55 mg/kg once a day (at 9 am) during the second week (tapering dose) and 1.1 mg/kg every other day (at 9 am) in the third week (alternate day therapy - tapering dose). In group II, immunosuppressive doses of prednisolone were administered orally (1.1 mg/kg) twice a day (at 9 am and 9 pm) for the first ten days, 0.75 mg/kg twice a day between 11th and 20th days, 0.55 mg/kg twice a day between the 21st and the 30th days, 0.25 mg/kg twice a day between the 31st and the 40th days, and 0.25 mg/kg once a day (at 9 am) for the last 10 days (tapering dose). No drug was administered to group III (control group).

B) SAMPLE COLLECTION

Blood samples were obtained from the vena cephalica antebraehii into plain silicone coated tubes. The blood sample were let clotting at room temperature and then centrifuged 1500 g for ten minutes at room temperature and were immediately stored at -20°C. The first sample was taken before drug administration (pre-treatment). Samples were collected on days 8, 15, and 22 in group I (at 9 am and/or 9 pm) and on days 11, 21, 31, 41, and 51 in group II (at 9 am and/or 9 pm). The last samples were collected 2 weeks after the end of treatments (at 9 am). Blood samples were also collected from group III (control group) at the same sample collection times than in groups I and II (i.e. on days 8, 11, 15, 21, 22, 31, 37, 41, 51 and 66).

Thyroid biopsy samples were surgically obtained from the one fourth of the left lobe just after blood sample collections under general anesthesia with xylazine (2 mg/kg) and ketamine (10 mg/kg). Thyroid biopsy samples were obtained on day 22 in group I (3 dogs) and group III (3 dogs), on day 51 in group II (3 dogs) and group III (3 dogs) and on day 37 in group I (3 dogs) and on day 66 in group II (3 dogs).

C) BIOCHEMICAL AND HISTOLOGICAL ANALYSIS

The samples were analyzed using 125I labeled RIA kits and levels of T₃ (Total Triiodothyronine®, Immunotech, Cat No: 1699), T₄ (Total Thyroxine®, Immunotech, Cat No: 1447), and fT₄ (T4 Libre Free T4®, Immunotech, Cat No: 1363.) were detected.

For the light microscopic examination, tissues were fixed in 10% formalin solution and cut at the thickness of 7 μm. The sections were further stained with uranyl acetate and lead citrate [21], and then examined under electron microscope (Carl Zeiss EM 9-S2).

D) STATISTICAL ANALYSIS

Data were analyzed using paired-t test and Student’s t test [7] and the differences were considered as significant when p values were less than 0.05.

The protocol was approved by the Ethics Committee of the Faculty of Veterinary Medicine, University of Ankara, Turkey.

Results

A) SERUM THYROID HORMON CONCENTRATIONS

The concentrations of T₃, T₄ and fT₄ in blood samples were summarized in Table I and II.

In control group (group III), the scattering of fT4 concentrations was weak and this biochemical marker was relatively stable during all the experiment. By contrast, serum T₃ and T₄...
concentrations presented a greater scattering and even marked fluctuations according to time were noticed for T3 concentrations at days 31 and 66.

In group I (anti-inflammatory doses of prednisolone: 2 X 0.55 mg / kg / day for the first week), marked and significant decreases of serum T3 and fT4 concentrations were evidenced on Day 8 in comparison to initial values (pre-treatment concentrations) (p < 0.05) and in comparison to control values obtained at the same time (p < 0.01) (Table I). Such important decreases of serum T3 and fT4 concentrations were also noticed in group II (immunosuppressive doses of prednisolone: 2 X 1.10 mg / kg / day for the first 10 days) in comparison to initial and control values (p < 0.05) during the first period (day 11) (Table II). Moreover, fT4 concentrations were more dramatically reduced in group II than in group I (Group I, day 8: 6.00 ± 0.39 pmol/l and group II, day 11: 4.23 ± 0.78 pmol/l; p < 0.05). Serum T3 concentrations decreased too on day 8 in group I and on day 11 in group II, but these variations were not statistically significant.

At day 21, T3 and fT4 concentrations were still diminished in comparison to pre-treatment values (p < 0.05) and in comparison to control values (p < 0.01 for T3 concentrations and p < 0.05 for fT4 concentrations) in group II (immunosuppressive doses of prednisolone: 2 X 0.75 mg / kg / day for 10 days) (Table II). At the same time, T4 concentrations were also significantly decreased from initial and control values (p < 0.05 and p < 0.01 respectively) in this group (Table II). By contrast, serum thyroid hormone concentrations significantly increased on day 15 in group I (Anti-inflammatory doses of prednisolone: 0.55 mg / kg / day during the second week) (p < 0.05) and they progressively declined again for reaching control values on day 22 (Table I). Fifteen days after the end of anti-inflammatory treatment, no obvious change in serum thyroid hormone concentrations was observed in the group I. Between the 21st and the 41st day in group II (immunosuppressive doses of prednisolone: 2 X 0.55 mg / kg / day between the 21st and the 30th day and 2 X 0.25 mg / kg / day between the 31st and the 40th day) serum T3, T4 and fT4 concentrations significantly rose again (p < 0.05) and became comparable to pre-treatment values.

Furthermore, when animals received a minimal dose of prednisolone (0.25 mg / kg / day) a rise of T3 concentrations in comparison to basal and control values (p < 0.05 and p < 0.01 respectively) was observed on day 51. This effect persisted on day 66 (p < 0.05 in comparison to initial values and p < 0.01 in comparison to control values) when dogs received no more prednisolone (Table II). At the same time, fT4 concentrations were weaker than those of group III (p < 0.05) although they were closed to pre-treatment values.

**B) THYROID MORPHOLOGY**

Light microscopic examination of biopsies in-group III revealed that the thyroid follicles were active in group III (figure 1). Lumen of the follicles was large and filled with colloid (K). In the two treated groups, inactive follicles were seen among the active follicles (figures 2 and 3 I). But the number of inactive follicles by microscopic field was greater in group II than in group I (p < 0.05). No picture of exocytosis was observed in dogs treated by prednisolone (groups I and II). However 2 weeks after the end of treatments, follicles in both groups (figure 4) appeared normal, but smaller

![Table 1](image-url)

Table 1: Evolution of serum T3, T4 and fT4 concentrations in dogs that received anti-inflammatory oral doses of prednisolone (group I: 2 X 0.55 mg / kg / day for the first week, 0.55 mg / kg / day during the second week and 1.1 mg / kg / alternate day in the third week) and in control dogs (group III). Results were expressed as means ± standard errors. Minimum and maximum values were indicated in parenthesis.

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than those observed in group III.

In electron microscopy of normal thyroid (group III), the follicle epithelial cells contained only few colloid droplets and several lysosomes (figure 5). In groups I and II, the number of colloid droplets increased (figure 6) and they fused together producing large colloidal areas in the cells (figure 7 K). It was noticed that lysosomes were very scarce (arrow) or absent. Two weeks after the last prednisolone administration, follicular epithelial cells in groups I and II appeared to be similar to the group III.

Discussion

Prednisolone has been frequently used for the treatment of various diseases in clinics. Usage of this drug in possible shorter periods and at lower doses is the rational approach to have minimum influence on glucocorticoids, which are naturally produced and released into the blood [17]. Whenever long-term usage is necessary, doses sufficient for treatment are gradually reduced and are preferentially given by oral route [1, 17]. But corticoids like prednisolone would also interfere with other endocrine functions and particularly with thyroid function [15]. However, the effects of anti-inflammatory or immunosuppressive doses of prednisolone administered to dogs according to classical clinical procedures on thyroid function were not explored in details.

Literature data and common application protocol of prednisolone were taken into consideration to decide upon the protocol scheme of prednisolone in this study [1]. Young adult dogs were used because T4 concentration drops with age and the responses of T4 to TSH and of TSH to TRH were reduced in old dogs [10]. Based on normal clinical examination, lack of anomaly in fecal examination and in urine analyses, the dogs used in our study were considered as in good health. They were nor fat neither cachectic, had good appetite, and presented healthy skin and hair coat. Besides, the mean serum T3, T4 and fT4 concentrations were included in normal range [11]. Study was started following 21 days, after period for adaptation to food and to new environment.

In the present study, early decreases of serum T3 and fT4...
concentrations were noticed in group I (day 8) and in group II (day 11) after the beginning of anti-inflammatory and immunosuppressive treatments with high doses of prednisolone. The effects of these high dosages on thyroid function have persisted until the 21st day with low serum T3, T4 and fT4 concentrations in group II. These results were similar to those previously reported by other researchers [12, 15]. When prednisolone doses were progressively reduced and/or administered in alternate day, rises in thyroid hormone concentrations were observed from the 15th day for group I and from the 31st day for group II. In dogs that received anti-inflammatory doses of prednisolone (group I), T3, T4 and fT4 returned more quickly closed to pre-treatment values. Fifteen days after the end of both treatments, T4 and fT4 concentrations were similar to control values, and even T3 concentrations were greater than initial values in group II. The depletion of thyroid function in our study was mainly evidenced in a non-invasive way by significant decreases in serum T3 and fT4 concentrations whereas changes in T4 concentrations were not statistically significant or were moderated (on day 21 in group II). These results suggest that the effects of both prednisolone regimen on the thyroid function are transient. In the same way, changes in serum T3, T4 and fT4 concentrations in patients with iatrogenic hyperadrenocorticism were improved following 2 weeks after the end of corticoid administration [16, 18]. In the same way, KEMPPAINEN et al [13] showed that anti-inflammatory doses of prednisolone for 35 days did not induce any statistically important modification in T4 concentrations in dogs. As a consequence, fT4 was a better marker than T4 for thyroid function and was independent from the transport capacity of plasma globulines [2]. As T4 is the principal hormone synthetised by thyroid gland [9], impairment in thyroid function would directly and early lead to fall serum fT4 concentrations. Because the intense fixation of T4 to serum proteins (albumin and specific globulines) slowed down the liver hormone catabolism [9, 13, 14], bound T4 persisted in plasma for a long time and serum T4 concentrations would be less responsive to variations in thyroid bio-synthesis. In dogs that received immunosuppressive doses of prednisolone (group II), significant decreases of T4 concentrations were transiently noticed on day 21 whereas T3 and fT4 concentrations were already altered on day 11. However, in other investigations [6, 20, 24], more durable variations of T4 concentrations have been reported and would be related to different proceedings of drug administration.

Table 2: Evolution of serum T3, T4 and fT4 concentrations in dogs that received immunosuppressive oral doses of prednisolone (group II: 2 X 1.1 mg / kg / day for the first 10 days, 2 X 0.75 mg / kg / day between the 11th and the 20th days, 2 X 0.55 mg / kg / day between the 21st and the 30th days, 2 X 0.25 mg / kg / day between the 31st and the 40th days and 0.25 mg / kg / day for the last 10 days) and in control dogs (group III). Results were expressed as means ± standard errors. Minimum and maximum values were indicated in parenthesis.

<table>
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<th>Days</th>
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<th>Group II</th>
<th>Group III</th>
<th>Group II</th>
<th>Group III</th>
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<td>1.56 ± 0.12a</td>
<td>22.50 ± 9.16</td>
<td>18.89 ± 5.96a</td>
<td>9.76 ± 2.27</td>
<td>10.24 ± 0.90a</td>
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<td>(1.26 - 2.20)</td>
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<td>(4.93 - 51.63)</td>
<td>(3.06 - 18.42)</td>
<td>(6.27 - 11.30)</td>
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<td>0.99 ± 0.11 *b</td>
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<td>(7.51 - 14.89)</td>
<td>(1.90 - 15.48)</td>
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<td>1.03 ± 0.07 **b</td>
<td>25.26 ± 5.21</td>
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* p < 0.05 and ** p < 0.01: differences between treated and control dogs.

a, b, c: different letters in the same column are significant comparing pre-treatment and treatment values.

KURTEDE (A) AND COLLABORATORS

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On the other hand, the collapse of $fT_4$ concentrations could also result from an acceleration of hormone catabolism with probable induction of liver cytochromes P450. Several drugs like diazepam and barbiturics are well known to interfere with hormone catabolism by this way [8, 9, 22]. But, because no data about prednisolone effect on cytochromes P450 implicated in the T3 and T4 catabolism was available, this hypothesis could be discarded.

In our study, changes in $fT_4$ concentrations were associated with decreases of serum T3 concentrations. MOORE et al. [16] observed no changes in the serum T3 concentration but decreases in serum T4 concentration, after administration of anti-inflammatory oral doses of prednisone for 5 weeks. A possible competition on the albumin binding sites between prednisolone or corticoids and thyroid hormones [4, 19, 22] could partially explain the modifications of T3 concentrations whereas T4 concentrations would be less quickly affected because of the greatest affinity of serum transport proteins for T4 [9, 14]. Moreover, the fall in thyroid T3 production and / or the reduced activity of 5’monoseiodase described in Cushing syndrome [19, 22] could be responsible for reducing the conversion of T3 into T4 and consequently for reducing serum T4 concentrations.

The impairment of thyroid function due to prednisolone administration is confirmed by morphologic examination of the gland. Indeed, inactive areas characterized by enlarged follicles with accumulation of colloid droplets in epithelial cells were frequently observed in thyroids from treated dogs (groups I and II). These results were in good agreement with previous studies on thyroid morphology [9, 19]. The remarkable low number of lysosomes in thyroids from treated dogs (groups I and II) suggested that the inhibition of lysozomal hydrolysis of coloids in follicle cells induced severe decreases of hormone release into the blood. Other studies [13, 23, 24] suggested that despite the accumulation of colloid in thyroid follicle epithelial cells after prednisolone administration, the decreases of the T3 and T4 concentrations could result in inhibition of lysozomal hydrolysis of colloid. Furthermore, previous studies in humans [9, 19] have reported that steroid anti-inflammatory drugs such as prednisolone directly acted on hypothalamo-hypophyseal axis by reducing release of hypophyseal hormones, and notably of TSH, and consequently by inducing a secondary hypothyroidism. The measurement of plasma TSH concentrations could confirm or infirm the occurrence of such a direct effect of corticoids on hypothalamo-hypophyseal axis in the dog.

However, prednisolone induced transient modifications of serum thyroid hormone concentrations with recovery and even overtaking pre-treatment values as soon as the initial prednisolone doses were reduced at least by 50% (in group I : 2 X 0.55 mg / kg / day to 1.1 mg / kg / alternate day - in group II : 2 x 1.1 mg / kg / day to 2 X 0.25 mg / kg / day) whereas in the same time, profound morphological changes were still observed in thyroid gland. In consequence, the obvious lack of correlation between serum thyroid hormone concentrations and morphological changes opened up the way to questions about the nature of adaptive mechanisms observed during prednisolone administration with anti-inflammatory
and immunosuppressive regimens. How can serum thyroid concentrations be restored despite continuous impairment of thyroid biosynthesis (evidenced by morphological changes)? Perhaps, the T₃ conversion into T₄, and the transport protein biosynthesis in the liver would be increased leading firstly to an accumulation of bound hormones which catabolism was slowed down, and secondly to the displacement of equilibrium between bound and free forms in favour for free hormones. In the same time, because the splitting up of prednisolone doses would reduce the direct inhibition of thyroid hormones, the adaptative response would be relevant until the end of treatment.

As a conclusion, prednisolone, a frequently used drug in clinics, affects directly the thyroid hormone biosynthesis by inhibition of lysosomal hydrolysis of colloid, leading to decrease serum T₃, T₄ and fT₄ concentrations. But, the prednisolone administration regimens (doses of 2.2 to 0.25 mg/kg/day and 1.1 mg/kg/48 hours intervals (tapering doses) for 50 days and doses of 1.1 to 0.55 mg/kg/day (tapering doses) for 21 days) induced only transient alterations of serum thyroid hormone concentrations and allowed relevant adaptive mechanisms (probably in hormone transport) to develop until the end of treatment.

References