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Influence of Dexamethasone Administration on Hematology, Biochemistry, and Thyroid Hormones in Dogs

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Abstract | Veterinary drug formulary includes many anti-inflammatory drugs, among them Glucocorticoids (GCs). This study evaluated the influence of dexamethasone parenterally (IM) on hematology, biochemistry, thyroid function in normal healthy dogs. Ten mongrel dogs were enrolled in this study, each dog received dexamethasone at a dose of 0.1 mg/kg once daily for 7 days then on an alternate day for 14 days. Blood samples were taken at day 0, day 7, and day 21 of the experiment for determination of CBC, ALT, ALP, Cholesterol, Serum total thyroxine (T4), free T4 (fT4), and thyroid-stimulating hormone (TSH). No significant changes in hematology were recorded throughout the experimental period. Elevation of ALT and ALP was recorded on day 7 and continue on day 21. Total T4 decreased significantly at day 7 and day 21. Free T4 showed a non-significant decrease at day 7 and day 21 compared to day 0 values, TSH showed a non-significant decrease at day 7, however, at day 21, TSH values were elevated to the level of day 0. Dexamethasone administration has an impact on the enzymatic activities of the liver. Administration of dexamethasone at a dosage of 0.1 mg /kg once daily for 7 days decreased total T4, while fT4 was unchanged, suggesting that fT4 may be less affected by daily dexamethasone administration. Administration of dexamethasone every other day meddled with TT4 but its effect on FT4 was minimum. Dexamethasone in this administrated dose has a little effect on serum TSH value.

Keywords | Dexamethasone, dogs, Thyroid hormones, ALP, Hematology.

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INTRODUCTION

In canine practice, many drugs are employed for their anti-inflammatory properties. These drugs might have an impact on hemato-biochemical and hormonal status in the body. Thyroid hormone status is known to be impacted by several factors among them drugs. These drugs working through modification of synthesis/secretion or have a direct influence on "hypothalamic-pituitary-thyroid Axis"; GCs – Exogenous or Endogenous- were known to influence thyroid hormones in dogs (Daminet and Ferguson, 2003; Nelson and Maggiore, 2020).

Glucocorticoids (GCs), an anti-inflammatory and immunosuppressive drug, used extensively in veterinary settings (Andrade et al., 2018). They were classified according to their effect on inflammation into rapid, intermediate, and long-acting (Torres et al., 2005). Numerous conditions benefit from GCs; either as an acute therapy, for instance: allergies, asthma, dermatologic conditions (allergic dermatoses, pemphigus) or as a chronic therapy: adrenal insufficiency, acquired thrombocytopenia, many inflammatory and neoplastic conditions (Plumb, 2018; Narang and Singh Preet, 2019). GCs have minimal effect on hematology (Bhavani et al., 2015) and varied hepatic enzymes activities alterations (Hinson et al., 2010).

Dexamethasone, a synthetic GCs, is known for its potency which was approximated to be about 5-10 times the potency of prednisolone (Derendorf et al., 1993; Andrade et al., 2018). Several studies showed the effect of anti-in-

flammatory/ immunosuppressive oral administration of prednisolone -short term and long term- on thyroid status in dogs either euthyroid or hypothyroid (Kurtdede et al., 2004; O'Neill et al., 2010). Though, it was postulated that the effect on the thyroid gland differs with formula, quantity, and route of administration (Kurtdede et al., 2004). The effect of prednisolone on thyroid status in dogs are well-documented (Daminet and Ferguson, 2003; Kurtdede et al., 2004; O'Neill et al., 2010) and the effect of topical administration of dexamethasone on thyroid function was reported but not as frequently (Gottschalk et al., 2011). However, the effect of dexamethasone parenteral administration on thyroid status was not extensively studied.

TT4 level is thought to elevate in small breeds dogs compared to larger ones with Grey-Hound dogs documented to have lower TT4 than other breeds (Hegstad-Davis et al., 2015). It was reported that age has no effect on thyroid hormones (Franklyn et al., 1985); however, Hegstad-Davis et al. (2015) showed that advances in age were linked to a reduction in TT4. Serum of intact females in anestrous and intact male was similar in thyroid function but females in disastrous have higher values and it was recommended to measure thyroid hormones during the anestrous phase in intact females (Hegstad-Davis et al., 2015).

This research was carried out to evaluate the effect of anti-inflammatory dosage of dexamethasone on hematology, serum biochemistry, and thyroid hormones in normal healthy dogs.

MATERIALS & METHODS

Ethical Approval

This study was performed in accordance with the ethical standards of the institution Animal Care and Use Committee, faculty of veterinary Medicine Cairo University, Egypt. This study was granted ethical approval # vetcu16072020183.

Experimental Animals

Ten mongrel dogs (5 males & 5 females) were enrolled in this experiment. Dogs aged between 1-3 years and weighing 15-20 kg. Females were selected in the anestrous phase to avoid discrepancies in thyroid hormones as reported by Hegstad-Davis et al. (2015). All dogs were clinically healthy, fecal and blood samples were taken from each dog to ensure they were parasitological-free. Dogs were kept for 21 days prior to the experiment for acclimatization. Each dog kept in a separate kennel, environmental conditions as temperature, humidity, photoperiod, and ventilation were kept constant throughout the experiment. A standard commercial diet was given twice daily, and ad libitum water was available.

Experimental Design

Each dog received a daily intramuscular (IM) injection of 0.1 mg\kg dexamethasone for one week (Ramsey, 2014; Plumb, 2018) followed by every alternate day for 2 weeks. For studying the effect of dexamethasone on hemato-biochemical parameters and thyroid hormones, a blood sample was collected from a cephalic vein in each dog, samples were collected at early morning at day 0 (Prior to administration of dexamethasone, serve as control), another two samples were collected at day 7 and day 21. Samples were collected on two tubes, EDTA containing tube for CBC determination using automated veterinary hematology analyzer and a plain tube for serum collection which was used to estimate cholesterol, ALT and ALP (Spectrum Diagnostics, Egypt) and TT4 (IDEXX Catalyst One), FT4 and TSH (Enzyme-linked fluorescent assay, VIDAS, Biomerieux). The health state of each dog was observed throughout the study and dogs were kept under observation for potential side effects with a slight increase in water intake and urine output as only observed changes. There was no observed change in body weight throughout the experimental period.

Statistical Analysis

Data were analyzed using one-way ANOVA, the comparison between Pre-administration and the post-administration data were made using SPSS statistic program version 16.0. P value ≤ 0.05 was considered significant.

RESULTS AND DISCUSSION

In canine medicine, GCs are indispensable anti-inflammatory/immunosuppressive drug with a potential effect on thyroid hormones (Nelson and Maggiore, 2020), though there are numerous papers studied the effect of prednisolone (one of GCs) on thyroid status in euthyroid dogs (Daminet and Ferguson, 2003; Kurtdede et al., 2004), scanty papers studied the effect of other GCs as dexamethasone on euthyroid dogs.

The main finding in our study is that the consecutive administration of dexamethasone using the intramuscular route for 7 days and alternate everyday approach has an impact on TT4, ALP, and ALT while FT4 and TSH changes were not as dramatic as those of TT4. It was hypothesized that the effect on the thyroid gland differs with formula, quantity, and route of administration (Kurtdede et al., 2004).

Patients Data

There were no observed changes in body weight throughout the experimental period. There was no difference in the obtained data from both sexes. Sex appeared to have insignificant effect on thyroid hormone levels as female

Table 1: Thyroid hormones status throughout experimental period in dog received daily intramuscular injection of 0.1 mg\kg dexamethasone for one week followed by every alternate day for 2 weeks. (N=10).

Parameters/Unit	Zero day	7 days	21 days
T4(µg/dl)	1.72 ± 0.19 [a]	1.09 ± 0.12* [b]	**1.08 ± 0.09* [b]**
FT4(ng/dl)	1.04 ± 0.08 [a]	0.87 ± 0.04 [a]	0.91 ± 0.07 [a]
TSH(mIU/L)	3.40 ± 0.51 [a]	2.50 ± 0 .68 [a]	3.24 ± 0.73 [a]

*Data represented as (Mean ±SE), P value ≤0.05. Different letters in the same raw are statistically significant with P value (P≤0.05). The same letters in the same raw are statistically not significant with P value (P≤0.05).

Table 2: Hematologic alterations throughout experimental period in dog received daily intramuscular injection of 0.1 mg\kg dexamethasone for one week followed by every alternate day for 2 weeks. (N=10).

Parameters/Unit	Zero day	7 days	21 days
RBCs (10^6/µl)	7.05 ± 0.24[a]	6.54 ± 0.20[a]	6.76 ± 0.25[a]
HB (g/dl)	16.14 ± 0.53[a]	14.32 ± 0.40[a]	14.20 ± 0.60[a]
PCV (%)	45.60 ± 1.21[a]	45.20 ± 0.97[a]	45.20 ± 1.16[a]
MCV (fl)	64.68 ± 1.25[a]	67.52 ± 0.68[a]	67.08 ± 1.39[a]
MCH (pg)	22.25 ± 0.48[a]	21.40 ± 0.40[a]	21.08 ± 0.26[a]
MCHC (g/dl)	33.20 ± 0.82[a]	31.68 ± 0.46[a]	32.05 ± 0.68[a]
WBCs (10^3/µl)	12.60 ± 0.93[a]	12.02 ± 0.82[a]	12.60 ± 0.93[a]
Neutrophil %	64.00 ± 0.41[a]	62.25 ± 0.63[a]	63.66 ± 0.88[a]
Lymphocyte %	17.00 ± 1.53[a]	18.33 ± 0.33[a]	18.66 ± 0.67[a]
Eosinophil %	2.40 ± 0.40[a]	2.00 ± 0.00[a]	2.00 ± 0.00[a]
Monocyte%	14.00 ± 2.08[a]	14.33 ± 1.76[a]	16.50 ± 1.50[a]
Platelets (10^3/µl)	205.40 ± 19.51[a]	214.60 ± 26.12[a]	192.80 ± 15.82[a]
RDWC%	12.00 ± 0.32[a]	12.20 ± 0.20[a]	12.40 ± 0.25[a]

Data represented as (Mean ±SE), P value ≤0.05. Different letters in the same raw are statistically significant with P value (P≤0.05). The same letters in the same raw are statistically not significant with P value (P≤0.05).

Table 3: Biochemical alterations throughout experimental period in dog received daily intramuscular injection of 0.1 mg\kg dexamethasone for one week followed by every alternate day for 2 weeks. (N=10).

Parameters/Unit	Zero day	7 day	21 day
ALP(U/l)	67.71 ± 7.10[a]	161.67 ± 4.48*[b]	180.67 ± 9.76*[b]
ALT(U/l)	22.40 ± 2.01[a]	47.33 ± 2.33*[b]	54.00 ± 9.19*[b]
Cholesterol(mg/dL)	155.40 ± 9.97[a]	193.20 ± 19.67[a]	190.80 ± 9.63[a]

Data represented as (Mean ±SE), P value ≤0.05. Different letters in the same raw are statistically significant with P value (P≤0.05). The same letters in the same raw are statistically not significant with P value (P≤0.05).

dogs were selected in the anestrous phase. It was reported that age has no effect on thyroid hormones (Franklyn et al.,1985); however, Hegstad-Davis et al. (2015), showed that age was linked to a reduction in TT4. Serum of intact female in anestrous and intact male was similar in thyroid function but female in disastrous have higher values and it was recommended to measure thyroid hormones during the anestrous phase in intact females (Hegstad-Davis et al., 2015).

Thyroid Hormones Status

TT4 showed a significant decrease at day 7 and day 21 compared to day 0 values. fT4 showed a non-significant decrease at day 7 and day 21 compared to day 0 values. TSH showed a non-significant decrease at day 7, however at day 21, TSH value was elevated to the level of day 0 (Table 1).

Dexamethasone administration caused a significant reduction in TT4 throughout the experimental period when compared to pre-administration values. fT4 showed a non-significant decrease throughout the experimental period. Though to our knowledge, few studies conducted using parenteral dexamethasone. other reports on an anti-inflammatory dose of Prednisolone PO showed a significant decrease of TT4 with no significant changes in ft4 and TSH at day 7 of administration but not at day 21 or day 28 (O'Neill et al., 2010). Furthermore, short term admin-

istration of an immunosuppressive dose of Prednisolone caused a significant reduction in TT4 starting from day 7 and reduction in fT4 at day 21 with no change in TSH in euthyroid dogs (Daminet et al., 1999). However, other reports showed a nonsignificant decrease in TT4 at day 8 with a significant decrease in fT4 at the same day but do not continue in day 15 of prednisolone administration at an anti-inflammatory dose (Kurtdede et al., 2004). The difference in results between dexamethasone administration and other reports discussing prednisolone could be attributed to the fact that dexamethasone is more potent than other GCs (Derendorf et al., 1993; Andrade et al., 2018), so its effect on TT4 was more remarkable and swift than prednisolone.

In other animals models, dexamethasone caused a significant reduction in serum fT4 24-hour post-administration then started to rise till 120 hours after administration and it was concluded that its effect is transitory on thyroid hormones (Narimane et al., 2017). In horses, topical use of dexamethasone caused a decrease in T4 after two days of application and it didn't return to normal baseline level after three weeks of withdrawal and they concluded that topical administration impacts thyroid hormones in normal horses (Abraham et al., 2011).

There was a non-significant decrease in TSH concentration at day 7 of dexamethasone administration, however, after alternate day to day administration, TSH values were numerically on a par with baseline values. In Cushing's syndrome, there is an inverse correlation between cortisol and TSH, however, GCs inhibit binding proteins of T4 and not TSH concentration (Abraham et al., 2011).

In this study, the chosen route of administration was parenteral route. Route of administration appears to have an apparent impact on thyroid hormones. In this study parenteral administration of dexamethasone caused a significant reduction of TT4 at day 7 of administration. In one report dealt with the effect of topical administration of dexamethasone, a similar reduction in TT4 was recorded though starting from day 12 to day 21 and oto-topical preparation caused a gradual decrease (Gottschalk et al., 2011). Differences in days could be attributed to the administration method. GCs appear to have an impact on thyroid profile as they may modify synthesis/secretion or have a direct effect on "hypothalamic-pituitary-thyroid Axis" (Daminet and Ferguson, 2003; Nelson and Maggiore, 2020).

Hematological Alterations

Hematological data are shown in table (2) and they were not changed statistically throughout the experimental period; these findings conceded with other reports (Bhavani et al., 2015). Other reports showed that hematologic parameters did not alter significantly except for eosinopenia in 18 dogs out of 28 dogs (Huang et al., 1999). Moreover, 'Bhavani et al. (2015) observed that hemogram stayed within normal range after steroids used to induce canine hyperadrenocorticism. An observed increase in platelets (Muñoz et al., 2017) and nucleated red cells were reported in other studies (Narang and Singh Preet, 2019). Changes caused by acute induction of GCs on hematologic values are temporary and for that, the expected alterations might not appear depending on the time of sampling in correlation with treatment administration (Willard et al., 2012).

Biochemical Alterations

Serum biochemical analysis showed a significant increase in ALT and ALP at day 7 and day 21 compared to day 0 values. Cholesterol showed a non-significant increase at day 7 and day 21 compared to day 0 values (Table 3). Changes in membrane permeability and/or necrosis of hepatocytes could cause an elevation in ALT, though the extent of damage is correlated with the level of elevation (Hinson et al., 2010). Exogenous administration of GCs causes an elevation in ALP isoenzyme via the production of corticosteroid-induced AP "CIALP" in the liver (Dorner et al., 1974; Solter et al., 1993). Though this increase is dose, duration, and drug-form dependent, in general, liver ALP is the one to increase in the first 7 days of GCs; CIALP begins to elevate at day 7 of treatment and continue to dominate in serum for one-month post-therapy (Johnson and Sherding, 2006). Cholesterol didn't alter significantly in this study, lipid metabolism partially controlled by thyroid hormones (Martínez-Sánchez et al., 2017), however, in hypothyroidism, elevated cholesterol was linked to decline in fraction clearance of cholesterol as a result of thyroid activity reduction (Shin and Osborne, 2003). It was showed that dexamethasone administration has minimal effect on "intrahepatic" triglycerides and dexamethasone showed to have some advantageous metabolic impact on HDL-cholesterol (Wang et al., 2012).

CONCLUSION

Parenteral administration of Dexamethasone has a direct impact on thyroid hormones mainly TT4. Hematologic values appear to be not dramatically affected but ALP and ALT elevated in response to dexamethasone administration. Free T4 was affected but to a lesser extend compared to TT4. Additionally, results from this study confirmed that monitoring canine TSH is useful when assessing thyroid function in dogs as it was the least affected by dexamethasone administration. This finding suggests that even a short course of daily anti-inflammatory dexamethasone can significantly decrease total T4 concentrations, so this drug should be cautiously evaluated when prescribed for hypothyroid dogs.

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CONFLICT OF INTEREST

Authors declared no conflict of interest

AUTHORS CONTRIBUTION

All authors contributed equally.

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