

Dose Dependent Effects of Lithium Carbonate on Rat Thyroid Hormones, Parathormon and Calcium Levels with Thyroid Tissue

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Submitted: 05.02.2020
Accepted: 05.07.2020

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Keywords: Ca levels;
lithium carbonate;
parathormone; rat; thyroid
hormones.



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ABSTRACT

Objective: The aim of this research was to investigate the effects of subacute use of lithium carbonate (Li_2CO_3), on serum T3, T4, thyroid stimulating hormone (TSH), parathyroid hormone (PTH) and calcium (Ca) levels and thyroid tissue. In addition, this research is important as one of the rare studies in which thyroid tissue was subjected to histological examination.

Methods: Thirty-two male Sprague Dawley rats were assigned into groups consisting of eight animals each, based on weight; Group 1: Sham control, Group 2: Li_2CO_3 +25 mg/kg, Group 3: Li_2CO_3 +50 mg/kg and Group 4: Li_2CO_3 +100 mg/kg. Li_2CO_3 was administered orally at varying concentrations, at 1 mL per day for 30 days. Serum samples were separated from blood obtained by intracardiac intervention. Serum T3, T4, TSH, PTH and Ca levels were measured by using an autoanalyzer and chemiluminescence. Thyroid tissue was examined under light microscopy after routine histopathological procedures.

Results: T3, T4, PTH and Ca levels increased in rats treated with high-dose Li_2CO_3 , whereas TSH levels were very low in all groups. In addition, thyroid tissue exhibited concentration-dependent histological alterations.

Conclusion: Li_2CO_3 , which was administered subacute high dose in rats, caused of increased T4 and T3 hormones levels, hyperparathyroidism and hypercalcemia in the early period. These results now need to be supported by further experimental and clinical studies.

INTRODUCTION

Although the mood stabilizing effects of lithium carbonate (Li_2CO_3) have long been known, over the last 40 years it has become a frequently employed agent in the treatment of bipolar disorders.^[1,2] It is also used as an adjunct drug in treatment-refractory depression.^[3] Previous research has demonstrated that lithium carbonate exhibits beneficial therapeutic effects by affecting excitatory and inhibitory mechanisms in the brain, although considering the complex pathophysiology of bipolar disorder, the exact effect mechanism is still not fully understood.^[4] The desired remission in bipolar disorder, a chronic and severe entity, can be achieved with appropriate therapeutic options.^[5] However, difficulties in drug selection and failure to achieve a response to the selected medication may result in the failure of the planned treatment.^[6]

Bipolar disorder is one of the principal psychological problems, affecting approximately 2.4% of the world pop-

ulation.^[7] Lithium occupies an important place among the main drugs used in prophylactic treatment, and is frequently employed in combination with anticonvulsants, antipsychotics, and antidepressants treatment.^[8,9] However, increasing blood-drug levels due to long-term lithium use, can result in dysfunction in several organs, especially the kidneys.^[10,11] Other significant problems include thyroid and parathyroid function anomalies.^[10,12] Lithium use-related impairment of thyroxine (T4) and triiodothyronine (T3) synthesis and secretion occurs in the form of mild hypofunction, but these may sometimes remain at normal levels.^[13] Increases have also rarely been reported.^[14]

One of the problems encountered with long-term lithium therapy is parathyroid function impairment, and an increase in circulating calcium.^[15,16] In previous studies, the hypothesis that kidney dysfunction occurring after chronic lithium use may be related to PTH and circulating calcium level.^[17,18] A previous study also showed that potential

deleterious conditions can be prevented by assessing PTH and calcium levels before and during lithium therapy.^[19]

The aim of this research was to investigate the endocrinological effects of experimental subacute lithium application at different concentrations on serum T3, T4, TSH, PTH and calcium levels and thyroid tissue and to reveal the relations between them. Our research is also important as one of the rare biochemical analyses of these hormones and histological examinations of thyroid tissue.

MATERIALS AND METHODS

Experimental animals

The research was conducted using cadaver tissue and sera left over from the study titled "An *In Vivo* and *In Vitro* Evaluation of the Lithium Comet Assay Used in the Treatment of Bipolar Disorder and Genotoxicity" under ethical committee permission No 2019/39 dated 29.11.2019.

Thirty-two male Sprague Dawley rats weighing 290 ± 10 g were employed for the purpose of biochemical and histological investigation. These were treated in line with the principles of the Guideline for the Care and Use of Laboratory Animals issued by the National Research Council and approved by the local ethical committee guideline. Prior to and during the course of the study, the rats were kept in standard plastic cages with straw floors, at a temperature of $22 \pm 2^\circ\text{C}$ in 55-65% humidity and under controlled lighting (a 12/12 hour light/dark cycle). Unrestricted access was permitted to standard rat chow and tap water. All animal experiments and procedures were conducted as required by national regulations concerning the care and use of laboratory animals. The study protocol was approved by the Recep Tayyip Erdogan University Institutional Ethical Committee, Turkey (No. 2018/56 dated 23.11.2018).

Chemicals

Lithium carbonate (Li_2CO_3) (Lithuril 300 mg 100 capsule) was obtained from Koçak Farma İlaç ve Kimya Sanayi A.Ş. (İstanbul, Turkey). Ketamine hydrochloride (Ketalar, 50 mg/kg, Pfizer İlaçları Ltd. Şti., İstanbul, Turkey) was used to anesthetize all animals, and xylazine hydrochloride (Rompun, 10 mg/kg, Bayer, Turkey) was administered for sedation. Other chemicals disposed for laboratory analyses were procured from Sigma Chemical Co. and Merck (Germany).

Experiment design

At the beginning of the study, rats were assigned into groups consisting of eight animals each, based on weight;

1. Sham control
2. Li_2CO_3 +25 mg/kg
3. Li_2CO_3 +50 mg/kg and
4. Li_2CO_3 +100 mg/kg

Li_2CO_3 Application

All procedures were carried out under sterile conditions. Following assignment into groups, those rats scheduled for drug administration received Li_2CO_3 at the concentrations described above in a total 1 mL volume every day for 30 days via the oral route. The sham control group received water in which the drug was dissolved at the same volume. Vital activities were checked every day during administration. At the end of the experiment, rats were sacrificed with the administration of high-dose anesthetic. Blood specimens collected by intracardiac intervention were placed into tubes without anticoagulant and centrifuged at 3000 g for 10 min at $+4^\circ\text{C}$ and then stored at -80°C until biochemical analysis. Thyroid tissue was placed into 10% neutral formalin for histopathological examination.

Biochemical analysis

Biochemical examinations were performed at the Recep Tayyip Erdogan University Training and Research Hospital Medical Biochemistry Department laboratory. Sera were vortexed, and FT3, FT4, TSH, PTH and Ca levels were measured by using the chemiluminescence technique on an Architect i2000 autoanalyzer (Abbott Diagnostics, USA).

Histological analysis

Rat thyroid tissue specimens were divided into 1.5 cm^3 pieces and fixed for 48 h in 10% neutral formalin solution (Sigma-Aldrich, Germany). Following the fixation procedure, the thyroid tissue specimens were dehydrated by being passed through increasing ethanol (Merck GmbH, Darmstadt, Germany) series, and then cleared in xylol solution (Merck, Darmstadt, Germany). Next, the thyroid tissues were embedded in paraffin blocks (Merck GmbH, Darmstadt, Germany). Sections $4\text{-}5 \mu\text{m}$ in thickness were then taken from these blocks, stained with Harris hematoxylin (Merck GmbH, Darmstadt, Germany) and Eosin G (Merck, Darmstadt, Germany), examined under a light microscope (Olympus Corp., BX51, Japan) and photographed using a digital camera (Olympus Co., DP71, Japan).

Semi-quantitative analysis

Histopathological findings observed in thyroid tissue sections were scored in line with previous studies involving histopathological analysis after thyroid toxicity, as shown in Table 2. Fifteen non-contiguous and randomly selected areas in each prepare were assessed by two independent histologists blinded to the study groups.

Quantitative analysis

Follicle surface area in the thyroid tissue sections was scored as shown in Figure 1 on Olympus DP2 software (Olympus Corp., Tokyo, Japan). Fifteen non-contiguous and randomly selected areas in each prepare were evaluated by two independent histologists blinded to the study groups.

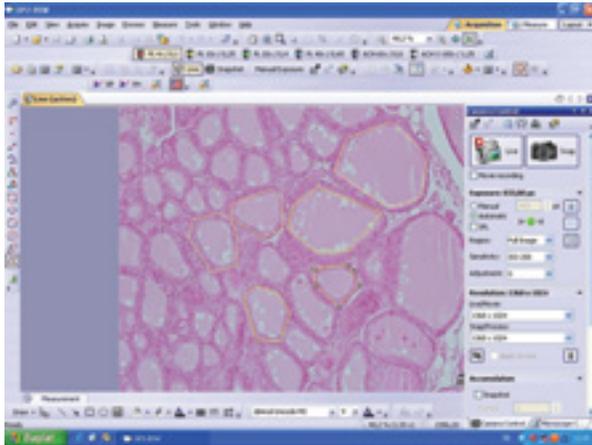


Figure 1. Representative light microscopic image of quantitative analysis of H&E-stained thyroid tissue sections.

Statistical analysis

All statistical analyses were performed on SPSS 18.0 (IBM, Armonk, NJ, USA) software. Data obtained from biochemical analyses were subjected to the Shapiro-Wilk test to evaluate normality of distribution and were calculated as mean±standard deviation. Intergroup comparisons were performed using One-Way ANOVA followed by the LSD test. Non-parametric data yielded by histopathological analyses were calculated as median, and 25% and 75% interquartile ranges. Intergroup differences were analyzed using the non-parametric Kruskal Wallis test followed by the Tamhane T2 test. P values<0.05 were regarded as statistically significant.

RESULTS

Biochemical results

Hormone levels were measured after 30 days of lithium carbonate administration. T4 levels were lower in the control group compared to the other study groups, although the difference was only statistically significant between the control group and Li_2CO_3 +100 mg/kg group ($p=0.001$; Table 1). On the other hand no statistically significant difference was detected between the control group and the other groups ($p>0.05$; Table 1).

Similarly, T3 levels only differed significantly between the control and Li_2CO_3 +100 mg/kg group ($p=0.03$; Table 1).

While differences were observed with the other groups, these not reach statistical significance ($p>0.05$; Table 1). Another parameter measured together with T4 and T3 hormone levels was TSH. However, this study is that serum TSH levels are below <0.01 uIU/mL in all groups. In the high dose lithium treated groups, the low serum TSH levels expected to occur due to the increase in serum thyroid hormone was observed in all groups in the study. However, low detection of TSH levels in the control group suggests that this decrease may have been due to the measurement method rather than the lithium effect.

Differences in PTH levels were determined between the study groups, but these were not statistically significant ($p>0.05$; Table 1).

A further parameter studied in the present research was Ca levels, and differences were again observed between the control and other groups. The differences between the Li_2CO_3 +100 mg/kg and the control and other study groups were statistically significant ($p=0.03$; Table 1).

Histopathological analysis results

Normal follicular cells, follicles and normal colloid contents were observed in the control group thyroid tissue sections (THDS median: 0 (0-1); Fig. 2; Table 3). Typical follicles were observed in thyroid tissue sections from Group 1 (THDS median: 2 (1-2); Fig. 3; Table 3). In contrast, Group

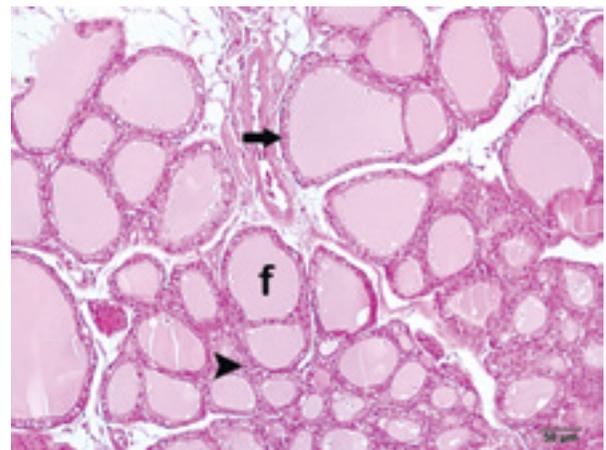


Figure 2. Representative light microscopic image of H&E-stained thyroid tissue sections. (x20): Control group sections exhibiting normal follicular cells (f) THDS median: 0 (0-1).

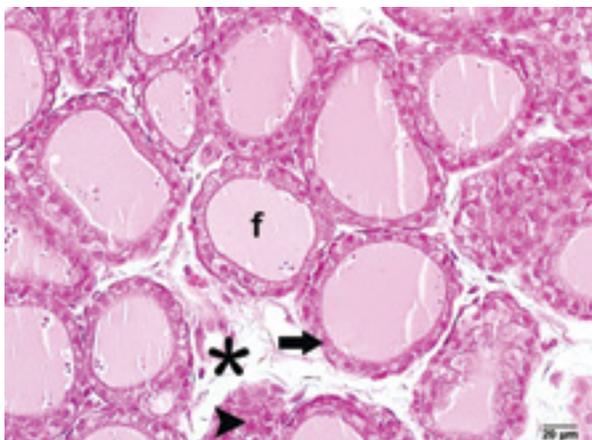
Table 1. Biochemical analysis scores

Study groups	Parameters measured			
	FT4 (ng/dL)	FT3 (pg/mL)	PTH (pg/mL)	Ca (mg/dL)
1. Control	1.02±0.10	1.18±0.14	4.80±1.89	9.38±0.29
2. Li_2CO_3 +25 mg/kg	1.09±0.13	1.50±0.41	7.92±3.35	9.87±0.24
3. Li_2CO_3 +50 mg/kg	1.09±0.42	1.42±0.33	8.33±7.04	9.71±0.26
4. Li_2CO_3 +100 mg/kg	1.25±0.57 ^a	1.60±0.29 ^b	11.70±7.06	10.25±0.48 ^a

^a: differs statistically significantly from the control group at $p=0.001$; ^b: differs statistically significantly from the control group at $p=0.03$.

Table 2. Thyroid histopathological damage scoring (THDS)

Finding	Score
Necrotic follicular cells	
0	less than <5%
1	between 6%-25%
2	between 26%-50%
3	More than 51%
Follicles with loss of colloid content	
0	less than <5%
1	between 6%-25%
2	between 26%-50%
3	More than 51%
Degenerative follicle (Necrotic follicular epithelial cells and loss of colloid content with in the follicular lumens)	
0	less than <5%
1	6%-25%
2	26%-50%
3	More than 51%

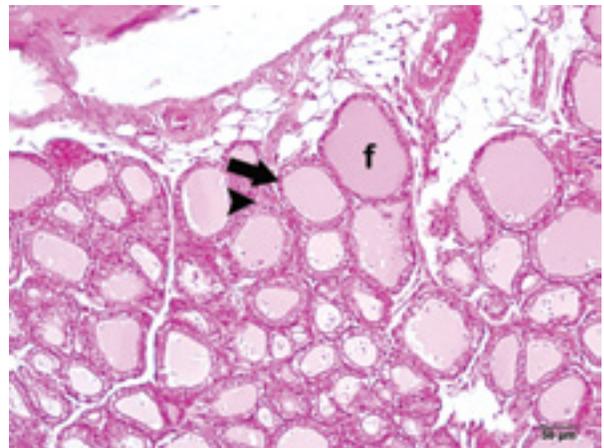
**Figure 3.** Representative light microscopic image of H&E-stained thyroid tissue sections. (x20): Sections from Group 1 exhibiting typical follicular cells and colloid content(f) THDS median: 2 (1-2).

2 thyroid tissue sections exhibited degenerative follicles with necrotic cells and loss of colloid content (THDS median: 3 (2-3); Fig. 4; Table 3). Degenerative follicles consisting of necrotic cells and with loss of colloid content were

Table 4. Thyroid follicle surface area measurements (mean±standard deviation)

Group	Follicle area (μm^2)
Control	31.312.99±12.541.40
Group 1	328.668.17±43.470.64 ^b
Group 2	307.564.97±46.055.91 ^c
Group 3	141.618.74±61.044.28 ^a

^ap=0.001; versus the control group; ^bp=0.001; versus Group 3; ^cp=0.001; versus Group 3; One-Way ANOVA-Bonferroni test.

**Figure 4.** Representative light microscopic image of H&E-stained thyroid tissue sections. (x20): Group 2 sections exhibiting typical follicular cells (f) THDS median: 3 (2-3).

observed in thyroid tissue sections from Group 3 (THDS median: 5.5 (5-6.5); Fig. 5; Table 3).

Semi-quantitative analysis results

We observed no difference in terms of necrotic follicular cells and follicles with cause loss of colloid between the control group and groups 1 and 2 (Fig. 2-4; Table 3). In contrast, degenerative follicles were found to have increased in Group 3 compared to the control group (Fig. 5; Table 3). We also determined an increase in necrotic follicular cells, follicles with loss of colloid content (degenerative follicles) in Group 3 section compared to the control group (Fig. 5; Table 3; p=0.002; p=0.000; p=0.001, respectively). In this study, pale colloid and resorption vacuoles were seen in the follicle lumens that increased depending on the dose.

Table 3. THDS results (median (25%-75% interquartile range))

Group	Necrotic follicular cells	Follicles with loss of colloid content	Degenerative follicles	THDS
Control group	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-1)
Group 1	1 (0.5-1)	0.5 (0-1)	0 (0-1)	2 (1-2)
Group 2	1 (1-1)	1 (0-1)	1 (0.5-1) ^c	3 (2-3) ^d
Group 3	2 (2-2.5) ^a	2 (2-2) ^b	1 (1-2) ^d	5.5 (5-6.5) ^b

^ap=0.002 versus the control group; ^bp=0.001 versus the control group; ^cp=0.05 versus the control group; ^dp=0.001 versus the control group; Kruskal Wallis/Tamhane T2 test.

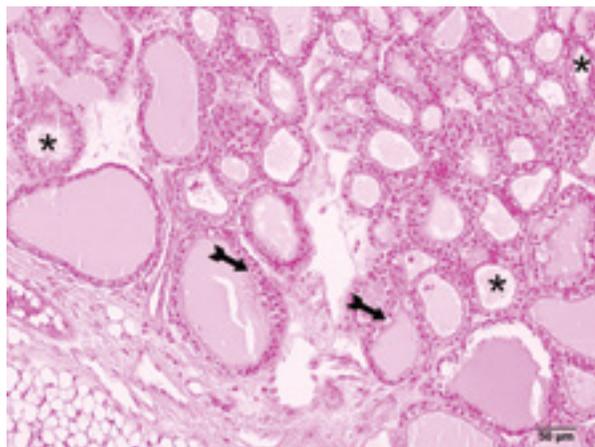


Figure 5. Representative light microscopic image of H&E-stained thyroid tissue sections. (x20): Sections from Group 3 showing Necrotic follicular epithelial cells with cytoplasmic vacuoles, follicles with pale or absence of colloid. (TDS median: 5.5 (5-6.5)).

Quantitative analysis results

No difference was determined between the control group and groups 1 and 2 in terms of follicle surface area (Fig. 2-4; Table 4). In contrast, follicle surface area decreased in Group 3 compared to the control group (Fig. 2-5; Table 4: $p=0.001$). Similarly, a significantly lower follicle surface area was observed in Group 3 than in groups 1 and 2 (Fig. 3-5; Table 4; $p=0.000$ and $p=0.001$, respectively).

DISCUSSION

This experimental study was performed in order to reveal the effects on the thyroid of different doses and concentrations of lithium carbonate, with its significant role in the treatment of bipolar disorder, one of the mood disorders. Monitoring blood-drug levels of lithium, with its narrow therapeutic index, during treatment is useful in terms of the taking of precautions against potential side-effects. In addition, this research will also contribute to determine the most appropriate rat dosage in experimental studies using lithium carbonate. Our experimental research showed the adverse effects of high-dose lithium administered at various doses.

In lithium toxicity, in addition to absence of clinical signs and asymptomatic conditions, nausea, vomiting, tremor, hyperreflexia, agitation, weakness and ataxia are regarded as indicating mild toxicity, drowsiness, stiffness, hypertension and hypotension as moderate toxicity, and myoclonus, cardiovascular collapse, seizure and coma as potentially severe intoxication.^[20] It has also been shown to cause nephrogenic diabetes insipidus, usually hypothyroidism, uncommonly hyperthyroidism.^[21-23]

Previous research has also reported hypothyroidism emerging with decreased thyroid hormone release after long-term lithium use as a common and important clinical finding, and that it may also rarely lead to hyperthyroidism.

^[24-29] Similarly in the present research, and consistent with previous studies, we observed that early period serum T4 and T3 levels increased in a dose-dependent manner. However, late stage of lithium will cause hypothyroidism.^[28] The presence of higher concentrations in thyroid tissue than in plasma following lithium intake explains the cause of the changes caused in thyroid functions.^[30] Although the mechanism involved in hyperthyroidism caused by lithium is not yet fully understood, the concentrations may have increased with a rebound effect in association with drug discontinuation, while studies have also reported serum thyroid elevation under the effects of follicle damage, auto-antibody synthesis and other underlying disease.^[25,29,31,32] In contrast, Kuman et al.^[33] reported no association between lithium therapy and hyperthyroidism, although Shine et al. suggested that hyperthyroidism may appear after treatment lasting several years.^[34] Additionally, the possibility of hyperthyroidism after lithium administration has also been shown in several case reports.^[31,35,36] In this study, however, there were no follicular damage and destruction, pale colloid and resorption vacuoles were seen in the follicle lumens that increased depending on the dose. These morphological findings are changes that can be observed in thyroid follicles in case of hyperfunction. Intake of lithium in high doses may cause an increase in follicular epithelial cell functions and this type of morphological changes in subacute period.

In our study, necrotic cells and follicles with loss of colloid content were detected in the early period after high dose lithium application, and an increase in serum thyroid hormone levels were detected in this process. However, it can be predicted that in the late period, hypothyroidism will occur with a decrease in serum level against this condition.

Another endocrinological problem seen with lithium therapy is parathyroid abnormalities.^[16,37] Previous research has revealed that the incidence of hyperparathyroidism increases with lithium therapy.^[38] Similarly, in the present experimental research we observed that the increase in PTH levels may be associated with the lithium dosage applied. These findings are consistent with previous research. In addition, calcium level elevation with high-dose administration was consistent with PTH, and this change may have altered the effect of lithium and calcium-sensing receptors. Livingstone C et al.^[22] also revealed that PTH levels change through a similar mechanism.^[39]

Kidney related side effects occur in approximately 20% of patients after long-term treatment with lithium.^[40] Hestbech et al.^[41] in a study conducted in patients with lithium intoxication, they revealed the development of chronic tubulointerstitial nephritis. Similarly, Markowitz et al.^[42] showed that kidney was affected by combined glomerular and tubulointerstitial damage following lithium toxicity. In addition, in experimental studies, it was stated that tubular lesion and dilatation occurred after lithium exposure. However, this mechanism is unclear.^[43] The risk of chronic kidney damage occurring in the later stages of chronic

lithium administration may contribute to the formation of hyperparathyroidism.^[39] It has been reported that the cause of hypercalcemia that occurs may also be the result of hyperparathyroidism.^[44] In this study, where subacute lithium was administered, we observed increased PTH and Ca levels similar to previous studies.

The limitation of this study is that serum TSH levels are below <0.01 uIU/mL in all groups. In the high dose lithium treated groups, the low serum TSH levels expected to occur due to the increase in serum thyroid hormone was observed in all groups in the study. This may be due to measurement methods. The amount of serum we obtained was not large enough to enable us to measure again. However, this research was performed as a pilot study to shed light on future research, and the findings now need to be confirmed by further studies considering intracellular pathways.

In conclusion, this study was an experimental investigation of the potential endocrinological outcomes of lithium therapy at different doses. In addition, our results suggest that lithium carbonate which was administered subacute high dose in rats, caused increased T4 and T3 hormones levels, hypercalcemia and hyperparathyroidism in the early period. However, hormone levels that increase temporarily in the short term following the application of lithium carbonate will decrease in the long term and may cause hypothyroidism. These data now need to be supported by further experimental and clinical research.

Acknowledgments

The author is profoundly grateful to Associate Professor Dr. Levent Tumkaya and Dr. Tolga Mercantepe of the Recep Tayyip Erdogan University Faculty of Medicine Histology and Embryology Department teaching staff for histological evaluations of thyroid tissues, and to Prof. Dr. Huseyin Avni Uydu of the Medical Biochemistry Department and again to Dr. Tolga Mercantepe for their advice concerning the statistical analyses.

Ethics Committee Approval

The study protocol was approved by the Recep Tayyip Erdogan University Institutional Ethical Committee, Turkey (No. 2019/39 dated 29.11.2019).

Peer-review

Internally peer-reviewed.

Conflict of Interest

None declared.

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Lityum Karbonatın Sıçan Tiroid Hormonları, Paratormon, Kalsiyum Seviyesi ve Tiroid Dokusu Üzerine Doza Bağlı Etkileri

Amaç: Bu araştırmanın amacı, subküt lityum karbonat (Li_2CO_3) kullanımının serum T3, T4, tiroid uyarıcı hormon (TSH), paratiroid hormon (PTH) ve kalsiyum düzeyleri ve tiroid dokusu üzerindeki etkilerini araştırmaktır. Ayrıca, bu araştırma tiroid dokusunun histolojik incelemeye tabi tutulduğu nadir çalışmalarından biri olarak önemlidir.

Gereç ve Yöntem: Otuz iki erkek Sprague Dawley sıçanı ağırlık bazında her biri sekiz hayvandan oluşan dört gruba ayrıldı; Grup 1: Sham kontrolü, Grup 2: $\text{Li}_2\text{CO}_3 + 25 \text{ mg/kg}$, Grup 3: $\text{Li}_2\text{CO}_3 + 50 \text{ mg/kg}$ ve Grup 4: $\text{Li}_2\text{CO}_3 + 100 \text{ mg/kg}$. Li_2CO_3 , 30 gün boyunca günde 1 ml olarak değişen konsantrasyonlarda oral yoldan uygulandı. Serum örnekleri intrakardiyak müdahale ile elde edilen kandan ayrıldı. Serum T3, T4, TSH, PTH ve Ca seviyeleri bir otoanalizör ve kemilüminesans kullanılarak ölçüldü. Tiroid dokusu rutin histopatolojik işlemlerden sonra ışık mikroskobu altında incelendi.

Bulgular: Yüksek doz Li_2CO_3 ile tedavi edilen sıçanlarda T3, T4, PTH ve Ca seviyeleri yükselirken, TSH düzeyleri tüm gruplarda çok düşüktü. Ek olarak, tiroid dokusu konsantrasyona bağlı histolojik değişiklikler sergiledi.

Sonuç: Sıçanlarda subküt yüksek doz uygulanan Li_2CO_3 erken dönemde T4 ve T3 hormon düzeylerinde artış, hiperparatiroidizm ve hiperkalsemiye neden olmuştur. Bu sonuçların artık daha ileri deneysel ve klinik çalışmalarla desteklenmesi gerekmektedir.

Anahtar Sözcükler: Ca seviyeleri; lityum karbonat; parathormon; sıçan; tiroid hormonları.