

THE BIOCHEMICAL AND HEMATOLOGICAL CHANGES
IN RATS FED BY LITHIUM CARBONATE

LİTYUM KARBONAT VERİLMİŞ SIÇANLARDA BİYOKİMYASAL
VE HEMOTOLOJİK PARAMETRELER

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Lithium is an effective drug used in bipolar affective disorders. The aim of this study was to investigate the changes in biochemical and haematological parameters. The experiments were carried on 20 Wistar-albino rats. The control group (10 male rats) was given lithium carbonate (1 mg kg⁻¹) by gavage to the rats in the morning and in the evening for 35 days.

The control group received only serum physiologic. After 35 days the rats were anaesthetized and 4-4.5 cc of blood was withdrawn from the left ventricle. The effects of lithium on biochemical parameters and also leukocyte and neutrophil counting in the rats were than evaluated.

Our results suggested that lithium has an important effect on biochemical and haematological parameters. For this reason it should be used with caution and during lithium therapy these parameters should be determined frequently.

Lityum, bipolar etkili bozukluklarda kullanılan etkili bir ilaçtır. Bu deneysel çalışmanın amacı biyokimyasal ve hematolojik parametreleri araştırmaktır. Deney grubu 20 Wistaralbino sıçanından, kontrol grubu ise 10 erkek sıçandan oluşmaktadır. Serum fizyolojik içinde hazırlanan lityum karbonat (1 mg.kg⁻¹) sıçanlara 35 gün boyunca sabah ve akşam gavaj yoluyla verilmiştir. Kontrol grubuna ise gavaj yoluyla sadece serum fizyolojik verilmiştir. 35 gün sonra sıçanlara anestezi uygulanarak, sol ventrikülerine girilmiş ve 4-4.5 cc kan alınmıştır. Alınan kan örneklerinde, lityumun biyokimyasal parametreler ile lökosit ve nötrofil sayımında yaptığı etkiler değerlendirildi.

Sonuçlardan anlaşıldığı gibi lityum, biyokimyasal ve hematolojik parametreler üzerinde yaptığı değişikliklerden dolayı dikkatle kullanılma ve lityum tedavisi boyunca bu parametreler sık sık kontrol edilmelidir.

Keywords: Lithium; Biological parameter; Blood cell count; Lithium side effect.

Anahtar sözcükler: Lityum; Biyokimyasal parametreler; Kan hücresi sayımı; Lityumun yan etkisi.

Introduction

The main objectives of lithium salts in psychiatry are sensory disorder, post depressive maintenance, schizoaffective

and schizophrenia therapies. It is also used in a wide range involving; Aggression control, drug and alcohol

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dependency, premenstrual syndromes, nutrition disorders, Addison's disease, hyperthyroidism, congenital neutropenia, neutropenia due to cancer chemotherapy, thrombocytopenia, trigeminal neuralgia, Parkinson's disease, FMF, ulcerative colitis (1).

Lithium is generally well absorbed when administered perorally. It takes 1-2 hours for the standard preparations to reach the maximum plasma concentration (2) and is distributed to whole body tissues. Lithium is not bound to plasma proteins and is distributed to the whole intracellular and extracellular fluids. The biological half life of the drug is 12-41 hours.

Lithium passes from the cell membranes by ion channels. It can pass easily from the sodium channels since it has an ion diameter similar to that of sodium.

Lithium causes changes in 5-hydroxytryptamine (5-HT) system and this effect has a role in the mechanism of lithium's action (3). Experimental studies have shown that short or prolonged usage of lithium increases the cerebral 5-HT turnover rate and levels of tryptophan and 5-hydroxyindolacetic acid (5-HIAA) (4).

The cure range of lithium is 0.50-1.2 mmol.L⁻¹ and doses higher than 1.4 mmol.L⁻¹ are toxic(5).

Recently, investigations related to lithium used in the treatment of various disorders have increased.

In our study, we evaluated the effects of lithium on biochemical parameters and blood neutrophil leukocyte levels.

Materials And Method

The experiments were carried on groups of 20 Wistar-albino adult male rats, weighting 280±50 g for a period of 19 weeks. The control group consisted of 10 male rats. All the rats were fed

with standard breed and tap water in private rat cages.

Lithium carbonate (1mg.kg⁻¹) in saline was given by gavage to the rats in the morning and evening at the same hours for 35 days. The control group received only serum physiologic.

On the 35th day of lithium carbonate administration the rats were anaesthetized intraperitoneally by pantothal sodium (35 mg.kg⁻¹) and their chests were opened and 4-4.5 cc of blood was taken from the left ventricle into the plain red vacotainers and the serum was separated by centrifugations for the biochemical tests. Blood was also taken into purple vacotainers containing EDTA for hematological cell counting.

The levels of serum glucose, blood urea nitrogen (BUN), creatinin, uric acid, calcium (Ca), phosphorus (P), total bilirubin, albumin were analyzed using Bayer Technican DAX-72 otomation system colorimetric method.

Alkalen phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine kinase (CK), gamma glutamyltransferase (GGT), cholesterol and triglyceride levels were also measured on the same system by the enzymatic methods. Na⁺, K⁺ and Cl⁻ levels were measured by the ion selective electrode method using the same system. Blood count and the formula were determined at the Bayer-Advia-120 Hematological System.

Results

Table 1 shows the levels of glucose, BUN, creatinin, uric acid, Na, K, Cl, Ca, inorganic phosphorus, alkalen phosphatase, AST, ALT, LDH, CK, GGT, triglycerides, cholesterol, total protein and albumin in the experimental group and the control group.

Table 2 shows the hematological values of the experimental and control group.

The results were evaluated by the Students -t-test.

Discussion

Lithium is an effective drug used in bipolar affective disorders(6). Having serious intoxications, the drug always

attracts great attention. Our experimental study showed significant results about the biochemical parameters and hematological changes obtained after therapeutic doses of lithium. Therefore, the patients having lithium cure are advised to pass blood biochemical tests at intervals(2).

Table 1 - The Biochemical Parameters

	Experimental Group	Control Group
Glucose (mg.dl ⁻¹)	155.60 ± 30.99*	90.50 ± 9.60
Bun (mg.dl ⁻¹)	19.75 ± 2.40**	15.02 ± 3.52
Creatinin (mg.dl ⁻¹)	49.50 ± 6.04*	1.06 ± 0.22
Ca (mg.dl ⁻¹)	9.89 ± 0.30***	9.51 ± 0.57
InP (mg.dl ⁻¹)	6.77 ± 0.66*	3.69 ± 0.53
Na (mmol.L ⁻¹)	140.20 ± 2.16***	139.52 ± 2.26
K (mmol.L ⁻¹)	5.18 ± 0.31**	4.49 ± 0.42
Alp (U.L ⁻¹)	196.80 ± 24.37*	77.42 ± 32.35
Ast (U.L ⁻¹)	146.40 ± 36.35*	22.77 ± 9.83
Alt (U.L ⁻¹)	80.65 ± 20.61*	30.37 ± 10.84
GGT U.L ⁻¹	3.30 ± 2.59**	56.50 ± 21.42
Ck (U.L ⁻¹)	839.25 ± 252.30*	117.42 ± 58.25
Ldh (U.L ⁻¹)	434.20 ± 95.69*	179.32 ± 34.20
Cholesterol (mg.dl ⁻¹)	46.60 ± 8.70	169.50 ± 18.92*
Triglycerides (mg.dl ⁻¹)	95.05 ± 53.74***	89.52 ± 40.10

* p < 0.0001 ** p < 0.001 *** insignificant

Table 2 - Hematological Values Of The Experimental And Control Group

	Experimental Group	Control Group
Leukocyte mm ³ . mlt ⁻¹	15.000 ± 1500	5600 ± 500
Neutrophil %	45 ± 3.0	21 ± 5

During lithium cure, primary hyperthyroidism increases(7). We have no significant results at the Ca levels of the experimental (n=20) and control (n=10) group rats. Mac T.W. et al. (8) explain led in their study that patients having lithium cure for 2 years showed increases at the serum PTH levels but no differences were observed at the serum Ca, alkalen phosphatase and inorganic phosphorus concentrations. Our results were similar with that of Mac T.W.'s about the Ca levels, but ALP and inorganic phosphorus (InP) levels were different. In the present

study, the InP and ALP levels significantly increased compared with those of the control group (p<0,0001).

In a study carried out by Tandon, A. (9) lithium administration to low protein fed rats resulted in significant increases in the hepatic GGT and glutation peroxydase (GPx) activities. In contrast, our results were significantly (p<0,001) were different as GGT levels of the experimental group were lower than those of the control group.

On the other hand, hepatic and serum levels of some showed alterations

parameters by lithium administration in the rats under different dietary protein regimens (10,11).

We think that the low GGT levels in our study was due to a decrease in hepatic GGT synthesis caused by lithium administration to rats with normal diet.

In the patients receiving lithium therapy, polyurea and polydypsia were seen showing that lithium has no effect on glomerular filtration (12). In patients receiving chronic lithium therapy, glomerular atrophy was seen which did not change the functional quality of the glomerules.

BUN and creatinin levels were also assayed in this work to evaluate the kidney functions and it was found that LiCO_3 causes increased BUN ($p < 0.001$) and creatinin ($p < 0,0001$) levels in the experimental group. According to these results, lithium, because of its possible effect on glomerular filtration, causes increases in the BUN and creatinin levels. No significant difference for sodium levels between the two groups was observed, yet the potassium levels were significantly increased in the experimental group.

The electrolyte levels have also been investigated for the treatment of bipolar affective disorders. Lithium acts by changing the electrolyte balance. It substitutes for sodium and changes calcium and magnesium distribution in cells, so it may play an important role in membran transport and enzyme activity (13,14).

We assume that the higher K levels obtained in this study could possibly be due to the effect of lithium on intracellular Na-K balance. In various studies, conflicting results about the effect of lithium on glucose metabolism have been published as; Vendsborg and Prytz (15) reported that chronic lithium therapy has no effect on glucose tolerance and serum

lipid levels. Yet in this study, glucose levels in the experimental group were higher than those of control group ($p < 0,0001$).

Transient hyperglycemia may occur during lithium intake due to the decrease in insulin secretion but this hyperglycemia disappears later (16, 17) and at the beginning of therapy, glucose tolerance may increase this condition. Increased glucose levels obtained in this study may be the consequence of transiently decreased insulin secretion. Triglyceride levels were in good agreement with Vendsborg's (15) study and it had no effect on triglyceride levels during chronic lithium therapy.

On the contrary, cholesterol levels in the experimental group were lower than the control group and were statistically significant ($p < 0,0001$).

In a study performed by Diebold (18) the changes in plasma lipid and lipoprotein levels during treatment with psychoactive drugs either alone or in combination with other drugs have been investigated.

Butyrophenones induce an increase in total cholesterol (TC), LDH levels, whereas tricyclics lead to an increase in TC, LDH, very low density lipoprotein (VLDL) levels. When these drugs are given in combination with lithium, lithium inhibits the increase in TC and LDH induced by butyrophenones and/or tricyclics. Decreased levels of cholesterol in our study may be the result of lithium inhibition.

Lithium usage may also cause changes at the hematological parameters. Leukocytosis mostly in polymorfonuclear neutrophil cell counting is seen after starting lithium cure. It was proposed that lithium carbonate administration may be used to control the leukopenia and infection after the chemotherapy (19,20).

Lithium usually causes mild and benign leukocytosis that persists during the therapy and disappears rapidly after the drug is withdrawn. These leukocytes are mature and functional.

In the present study leukocyte and neutrophil counting in the experimental group was significantly higher than those of the control group ($p < 0,001$). The leukocytosis was probably due to an increase in neutrophil granulocytes and this increase is in good agreement with the literature (20).

Consequently, we observed that biochemical and hematological parameters significantly increased in the experimental group, after 35 days of lithium carbonate therapy. For this reason, we suggest that biochemical parameters should be determined by intervals during chronic lithium carbonate treatment, because of its side effects. Also it should be used with extreme caution.

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