Lithium-Induced Alterations in Parathormone Function in Patients with Bipolar Disorder

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ABSTRACT:
LITHIUM-INDUCED ALTERATIONS IN PARATHORMONE FUNCTION IN PATIENTS WITH BIPOLAR DISORDER

Objective: Lithium carbonate may affect calcium metabolism and alter parathyroid physiology. The purpose of this study was to test the hypothesis that long-term lithium treatment can induce alterations in serum total calcium and biologically active (intact) parathormone (PTH) levels in euthymic bipolar patients. **Method:** Serum total calcium levels were measured with standard autoanalyzer techniques, and intact PTH (iPTH) levels were assessed by RIA in 10 lithium-naive (mean age±SD: 34.50±4.85) and 15 long-term lithium treated (mean age±SD: 34.46±10.16) bipolar patients. **Results:** Both serum total calcium and iPTH levels were found significantly higher in the lithium treated group compared to lithium-naïve group and there was a positive correlation between these two biochemical variables. **Conclusion:** These data demonstrate that long-term lithium treatment may alter serum calcium and PTH activity.

Key words: lithium, parathormone, calcium, bipolar disorder

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ÖZET:
BİPOLAR BOZUKLUĞU OLAN HASTALARDA LİTYUMUN YOL AÇTIĞI PARATHORMON FONKSİYON DEĞİŞİKLİKLERİ

Amaç: Lityum karbonat kalsiyum metabolizmasını ve paratiroid fizyolojisini etkileyebilir. Bu çalışmanın amacı ötimik bipolar hastalarda uzun süreli lityum tedavisinin serum total kalsiyum ve biyolojik olarak aktif (intakt) parathormon (PTH) düzeylerini değiştirebileceği hipotezini araştırmaktı. **Yöntem:** Bu amaçla, 10 hiç lityum kullanmamış (yaş ortalaması±SS: 34.50±4.85) ve 15 uzun süredir lityum kullanmakta olan (yaş ortalaması±SS: 34.46±10.16) bipolar hastanın serum total kalsiyum ve intakt parathormon (iPTH) düzeyleri sırasıyla standart otoanalizer ve RIA teknikleri ile ölçüldü. **Bulgular:** Uzun süreli lityum tedavisi almakta olan hastalarda lityum kullanmamış hastalara göre serum total kalsiyum ve iPTH değerlerinin her ikisinin de birbiriyle ilişkili olarak yüksek olduğu bulundu. **Sonuç:** Bu bulgular uzun süreli lityum tedavisinin, serum kalsiyum PTH fonksiyonlarını değiştirebileceğini ortaya koymaktadır.

Anahtar sözcükler: lityum, parathormon, kalsiyum, bipolar bozukluk

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INTRODUCTION

Since lithium (Li) can prevent the swings in mood, it is widely used in the treatment of bipolar mood disorders. It is estimated that in many developed countries 0.1% of the population is receiving lithium therapy (1). Cross-sectional studies of patients on lithium carbonate have revealed that calcium (Ca) and parathormone (PTH) levels have been elevated above the normal range in anywhere from 12-25% of these patients (2,3,4). PTH is known to increase both bone formation and resorption. In addition to its renal and osseous effects, the lithium ion also seems to have an effect on parathyroid tissue (5,6). The initial report of hyperparathyroidism associated with lithium carbonate treatment in 1973 led to a number of subsequent reports (7). Several months to several years are needed for lithium inducing primary hyperparathyroidism (8). However, it is not clear whether lithium initiates disease or promotes underlying hyperparathyroidism. There is no consensus on the prevalence, severity and mechanism of lithium-induced parathyroid dysfunction (1). Hyperparathyroidism generally presents as a mild biochemical disturbance without significant clinical manifestations (9). In this study, we aimed to test the hypothesis that long-term lithium treatment can induce alterations in serum total calcium (Ca) and biologically active (intact) PTH (iPTH) in euthymic bipolar patients.

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METHODS

Subjects

Fifteen euthymic bipolar patients (6 females, 9 males; mean±SD age: 34.46±10.16) on long-term lithium carbonate treatment for more than 6 months (mean duration of lithium treatment±SD: 48.93±39.01, range: 6-120 months) and 10 lithium-naïve euthymic bipolar patients (4 females, 6 males; mean±SD age: 34.50±4.85) who met the DSM-IV criteria for bipolar I disorder (10) were included in the study. The investigations were carried out mostly on an outpatient basis. The subjects were on no other medication known to affect Ca metabolism. Before enrolment, each subject underwent a physical examination and a laboratory evaluation that included a multichannel serum chemistry analysis and complete blood count, an iPTH level and a TSH level. To avoid any confounding effect of obesity on the PTH axis, all subjects had a body mass index (weight in kilograms divided by height in meters squared) of less than 30. Informed written consent was obtained from each subject before participation. This study was approved by the local ethics committee.

Procedure

A single fasting morning blood specimen was obtained between 07.00-08.00 a.m. after 10-12 h after the previous lithium dose. Venous blood was drawn into an ice-cold heparinized tube and centrifugated at 4°C. Serum Ca was determined by standard autoanalyser techniques and serum lithium was measured by atomic absorption spectroscopy. The remaining serum was frozen and stored at -70°C until the time of iPTH analysis. iPTH was measured by RIA (Diagnostic Systems Laboratories, Inc. US. Intact PTH kits). The lowest sensitivity limit was 12 pg/ml at 95% confidence level; intra-assay and inter-assay coefficients of variation were 3.5% and 5.2%, respectively; and normal range was 9-55 pg/ml.

Statistical Analysis

Mann-Whitney U test was used to compare the variables of the two groups. To investigate the relationships between PTH, Li and Ca values, we performed Pearson's correlation analysis. Significance was indicated for $p<0.05$.

RESULTS

As shown in table 1, there was no significant difference in mean age or duration of illness between the two groups studied. The mean±SD duration of Li use was 48.93±39.01 months in the Li-treated group. Serum creatinine and TSH levels were not sig-

Tablo 1. Clinical variables of the bipolar patients on lithium and lithium-naive

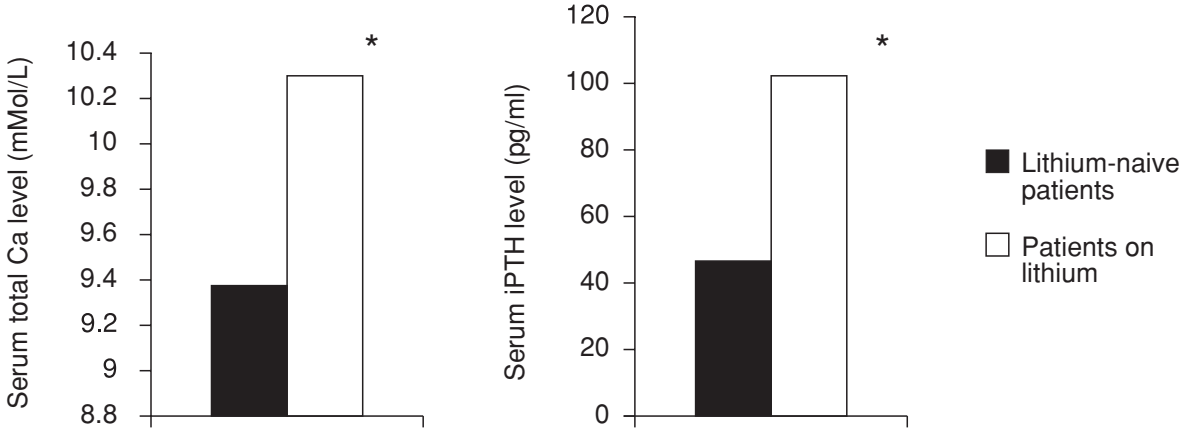
Clinical variables	Lithium-naive patients (n=10)		Patients on lithium (n=15)	
	Mean	SD	Mean	SD
Age	34.50	4.85	34.46	10.16
Duration of illness (year)	10.10	6.08	10.33	5.77
Number of episodes	7.46	5.26	9.00	8.29
Duration of lithium treatment (month)	-	-	48.93	39.01

Tablo 2. Biochemical variables of the two bipolar patient groups

Biochemical variables	Lithium-naive patients (n=10)		Patients on lithium (n=15)	
	Mean	SD	Mean	SD
Serum Li level (mMol/L)	-	-	0.72	0.15
Plasma creatinine level (mg/dl)	0.88	0.30	0.86	0.17
Serum total Ca level (mMol/L)	9.36	0.18	10.30[a]	1.15
Serum iPTH level (pg/ml)	46.71	41.82	102.05[b]	68.74

a: Significantly different from the lithium-naive patients ($U=23.5$, $p<0.05$)
b: Significantly different from the lithium-naive patients ($U=35.0$, $p<0.05$)

Figure 1. Serum total Ca and iPTH values of the bipolar patients.



*: Significantly different from the lithium-naive patients

nificantly different between the two groups. However, serum total Ca and iPTH levels were significantly higher in the Li-treated group (U=23.5, p<0.05 and U=35.0, p<0.05, respectively) (table 2, figure 1). There was a significant positive correlation between the iPTH and total Ca values in the Li-treated group (r=0.53, p<0.05).

DISCUSSION

Our data show significantly increased serum iPTH levels correlated with elevated total Ca levels in the bipolar patients on long-term Li treatment compared to the Li-naïve bipolar patients. Increased serum total Ca, ionised Ca (Cai) and iPTH concentrations have been reported in the patients taking Li in the previous studies (1,2,3,9,11). However, there are some papers reporting that Li causes an increase in serum Ca levels but not hyperparathyroidism (4). We also found a positive correlation between serum iPTH and total Ca values, but we could not study ionised Ca levels, a better indicator of serum Ca values. Some authors reported a negative correlation between ionised Ca and iPTH values and explained this relationship in a way that Ca was shifted to the right of normal during the lithium treatment (12,13). The data on the effects of Li on baseline serum PTH and Ca levels are conflicting. The fact that many studies failed to measure Cai levels, the primary modulator of PTH secretion, or used older assays that lacked the sensitivity and specifity needed to determine the iPTH molecule can explain these discrepant results. Furthermore, the facts that iPTH has a rapid half-life of disappearance and is secreted episodically and that Li affecting biological rhythms strongly (11) may lead to a time effect on PTH secretion may be other factors contributing to the discrepancies.

Kallner et al. (1995), who investigated the patients taking lithium for 1-30 years, have reported that elevated serum Cai was found in 25% and elevated serum iPTH in 23% of the Li-treated patients (3). The association between the treatment with lithium and PTH is unlikely to be a chance, but the exact mechanism is still unknown. The demonstration that Li acutely stimulates PTH release in human and animal parathyroid glands suggests that the hypercalcemia and/or elevated PTH levels that occur in some patients taking lithium might be directly related to the therapy rather than coincidental primary hyperparathyroidism (14,15). Nordenström et al. (1992) proposed that lithium-associated hyperparathyroidism might be of two types (16):

1. The form of early onset, which may be a sign of an activated incipient parathyroid adenoma,

2. The form of late onset, which is the result of chronic stimulation of the parenchymal mass, which results in hyperplasia.

We also consider that increased iPTH values are not due to a decrease in renal function since serum creatinine is not higher in the long-term Li treatment group compared to that of the controls, as previously suggested by some authors (1,3,11). However, some authors suggested that the hyperparathy-

roidism following Li treatment might be a consequence of reduced renal Ca reabsorbtion (17). Another possible mechanism that may account for Li-induced hypercalcemia has been suggested that Li could have a sensitising effect on bone resorption, but the studies did not confirm consistently this idea (18,19).

How long-term Li administration could cause hyperparathyroidism is unknown. Studies in vitro have demonstrated an increase in PTH secretion within 10 minutes following exposure to Li, suggesting that Li-induced changes in Ca-regulated PTH release take place rapidly (20). In humans, it has been reported that several months to several years are necessary for lithium inducing primary hyperparathyroidism (8).

Many Li-induced endocrinological side effects are thought to stem from cyclic adenosine monophosphate (cAMP) inhibition (9,21). The observed alteration in PTH dynamics and reduction in Ca secretion in patients on Li therapy could be caused by an effect of Li on Ca receptor signal transduction system of the parathyroid gland and kidney as in autosomal dominant syndrome of familial hypocalciuric hypercalcemia (22).

Most studies indicate that the discontinuation of Li leads to normalisation of serum Ca and iPTH levels (23), and Li-induced hyperparathyroidism has been generally considered to be without clinical significance (24). However, little or no significant change of persistent hyperparathyroidism has also been reported (25,26). It has been suggested that surgery might also be considered in patients with persistent hyperparathyroidism (9,13,21). Hypercalcemic hyperparathyroidism may exacerbate mental symptoms and reduce the effectiveness of Li in controlling affective symptoms (5,15).

In conclusion, our study documents a clear alteration in iPTH function manifesting itself as a secondary hyperparathyroidism in bipolar patients on long-term Li treatment compared to the Li-naïve bipolar patients and also emphasizes the need for the measurement of a baseline serum Ca, serum iPTH level and bone-mineral density in all patients before initiating their Li treatment, and routine periodic measurements of them as long as patients continue the treatment with Li. Nevertheless, prospective studies of the incidence of parathyroid adenoma formation, bone-mass, and fracture incidence are clearly needed.

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