

Effects of Long- and Short-Term Lithium Treatment on Kidney Functioning in Patients with Bipolar Mood Disorder

M. Tayfun Turan M.D.¹, Ertuğrul Eşel M.D.¹, Bülent Tokgöz M.D.²,
Suat Sabri Aslan M.D.³, Seher Sofuoğlu M.D.¹, Cengiz Utaş M.D.²,

ABSTRACT:

EFFECTS OF LONG- AND SHORT-TERM LITHIUM TREATMENT ON KIDNEY FUNCTIONING IN PATIENTS WITH BIPOLAR MOOD DISORDER

Objective: Lithium carbonate (Li) has been reported to be able to cause some reversible functional changes in the kidney. In this study, we aimed to investigate whether the duration of Li treatment is the primary determinant of the changes in renal functioning due to the Li treatment. For this purpose, we compared renal indices of the patients who were Li-naïve, and on short- and long-term Li treatments. **Methods:** Ten Li-naïve (mean age±SD: 34.50±4.85), 10 short-term (mean age±SD: 31.77±7.61) and 10 long-term (mean age±SD: 36.60±10.15) Li-treated bipolar patients were included in the study. Serum BUN and creatinine, urine creatinine levels, creatinine clearance, urine osmolality before and after 8-h water deprivation and urine osmolality after desmopressin injection were measured in all patients. Statistical comparisons of the renal values of the groups were carried out with one-way ANOVA. **Results:** Serum BUN and creatinine levels were within the normal limits and not statistically different among the groups. Creatinine clearance of the long-term Li-treated group was significantly lower than both that of the Li-naïve group and that of the short-term Li-treated group. After 8-h water deprivation and also after desmopressin injection, no difference was found among the groups in terms of urine osmolality. However, when each patient was evaluated individually in terms of their renal concentrating ability, partial nephrogenic diabetes insipidus was diagnosed in 4 patients on long-term and in 2 patients on short-term Li-treatment. To our surprise, hypothalamic diabetes insipidus was also diagnosed in other 2 patients on long-term Li-treatment. **Conclusion:** These results demonstrate that long-term Li treatment may cause impairment in renal concentrating ability some of which may originate from the effects of Li on vasopressin on hypothalamic level, and a decrease in glomerular filtration rate. In the light of these data, we can conclude that the duration of Li treatment is one of the main determinants of Li-induced renal changes in bipolar patients.

Key words: lithium, renal concentrating ability, creatinine clearance, diabetes insipidus, bipolar mood disorder

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ÖZET:

İKİ UÇLU DUYGUDURUM BOZUKLUKLULU HASTALARDA KISA VE UZUN SÜRELİ LİTYUM TEDAVİSİNİN BÖBREK FONKSİYONLARI ÜZERİNE ETKİSİ

Amaç: Lityum karbonat (Li)'in böbrek üzerinde çoğunlukla geri dönüşümlü olan bazı işlevsel değişikliklere neden olabildiği bildirilmiştir. Bu çalışmada, lityuma bağlı böbrek işlev değişikliklerinin asıl belirleyici faktörünün Li'un kullanma süresi olup olmadığını araştırmak istedik. Bu amaçla, henüz hiç Li kullanmamış, ve kısa ve uzun süredir Li kullanmakta olan hastalardaki böbrek değişkenlerini karşılaştırdık. **Yöntem:** On Li kullanmamış (yaş ortalaması±SS: 34.50±4.85), 10 kısa süreli (yaş ortalaması±SS: 31.77±7.61) ve 10 uzun süreli (yaş ortalaması±SS: 36.60±10.15) Li tedavisinde olan bipolar hasta çalışmaya alındı. Bütün hastalarda serum BUN ve kreatinin, idrar kreatinin düzeyleri, kreatinin klirensi, 8 saatlik su kısıtlaması öncesi ve sonrasında ve desmopressin verildikten sonra idrar osmolalitesi ölçümleri yapıldı. Verilerin gruplar arasındaki istatistiksel karşılaştırması için tek yönlü ANOVA kullanıldı. **Bulgular:** Serum BUN ve kreatinin düzeyleri bütün hastalarda normal sınırlar içindeydi ve gruplar arasında istatistiksel olarak anlamlı bir farklılık yoktu. Uzun süreli Li grubunda kreatinin klirensi hem Li kullanmamış, hem de kısa süreli Li grubununkinden anlamlı derecede düşüktü. 8 saatlik su kısıtlaması ve desmopressin enjeksiyonundan sonra idrar osmolalitesi bakımından gruplar arasında anlamlı bir farklılık bulunmadı. Ancak, her bir hasta tek tek böbrek konsantrasyon yeteneği bakımından değerlendirildiğinde, uzun süreli Li grubundaki 4 hasta ve kısa süreli Li grubundaki 2 hastada kısmi (parsiyel) nefrojenik diabetes insipidus tespit edildi. Ayrıca uzun süreli Li grubundaki 2 hastada hipotalamik diabetes insipidus saptanması ilginçti. **Sonuç:** Bulgularımız Li kullanma süresinin böbrek fonksiyonlarında oluşacak değişikliklerde önemli bir faktör olduğunu, uzun süreli Li kullanan hastaların bir kısmında sadece böbreğin vazopressine direnç mekanizmasıyla değil, aynı zamanda vazopressinin hipotalamik düzeyde de etkilenebileceğini sonucunda diabetes insipidus gelişebileceğini ortaya koymaktadır.

Anahtar sözcükler: lityum, böbrek konsantrasyon yeteneği, kreatinin klirensi, diabetes insipidus, iki uçlu duygudurum bozukluğu.

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INTRODUCTION

Lithium (Li) has been proved to be effective in acute and prophylactic treatments of bipolar

mood disorder. Li may cause functional changes in kidney, which have been reported to be typically benign and reversible (1). One of the well-documented renal side effects of Li is polyuria. Li-induced

¹Erciyes Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı, ²Erciyes Üniversitesi Tıp Fakültesi Nefroloji Bilim Dalı, ³Kayseri Devlet Hastanesi Psikiyatri Kliniği

Yazışma Adresi / Address reprint requests to: Dr. M Tayfun Turan, Erciyes Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı, Talas Yolu, 38039-Kayseri
Tel/Fax: +90 (352) 437 57 02 E-mail: tayfunturan@hotmail.com

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polyuria is associated with impaired renal concentrating ability, which is possibly due to a resistance of the collecting ducts to anti-diuretic hormone (ADH) (2, 3). However, deterioration in glomerular filtration rate (GFR) has rarely been reported (4). The polyuria and polydipsia observed on maintenance of Li treatment are generally considered to be harmless and reversible (5). In support of this idea, clinical studies showed that administration of ADH exerts little or no effect on the lithium-induced reduction in renal concentrating ability (2,3). Li-induced impairment in renal concentrating ability has been reported to be associated with a longer duration of Li treatment and higher plasma Li levels (6), or a multiple daily dosing schedule (7,8).

In humans, precise site of the inhibitory effect of Li on the action of ADH is thought to be the distal tubular cells, which is likely to be at the level of ADH-sensitive adenylate cyclase activity (9). Animal studies have confirmed that Li might affect ADH-induced generation of cyclic AMP in both distal and proximal tubules (10). In addition to this, it has been reported that the production of ADH might also be inhibited by Li so that the condition will be with mixed renal and hypothalamic origin (11).

In this study, we aimed to test the hypothesis that the duration of Li treatment might be the pri-

mary determinant of the changes in renal functioning due to Li treatment. For this purpose, we compared renal indices of the patients who were Li-naïve, and on short- and long-term Li treatments.

Methods

Subjects

Thirty patients (17 males, 13 females) fully meeting the DSM-IV criteria for bipolar affective disorder were included in the study. Ten of them (mean age \pm SD: 34.50 \pm 4.85, range: 27-41 years) were Li-naïve but candidate for Li treatment, 10 of them (mean age \pm SD: 31.77 \pm 7.61, range: 22-45 years) were on short-term (\leq 3 years, mean duration of Li treatment \pm SD: 15.77 \pm 8.64 months, range: 6-36 months) Li maintenance treatment and 10 of them (mean age \pm SD: 36.60 \pm 10.15, range: 21-59 years) were on long-term ($>$ 3years, mean duration of Li treatment \pm SD: 79.60 \pm 23.95 months, range: 48-120 months) Li maintenance treatment (table 1).

All patients were non-rapid cycling and in a euthymic stable mood state during the study and the patients' symptoms were assessed with the Schedule of Affective Disorder Rating Scale (SADS) on the day of the renal functioning tests performed.

Table 1. The comparison of clinical and renal variables of the Li-naïve, short and long-term lithium-treated bipolar patients

	Short-term Li-treated group (n=10)		Long-term Li-treated group (n=10)		Li-naïve group (n=10)	
	Mean	SD	Mean	SD	Mean	SD
• Age (years)	31.77	7.61	36.60	10.15	4.50	4.85
• Serum Li concentration (mM/L)	0.71	0.10	0.68	0.20	-	-
• Duration of Li treatment (months)	15.77	8.64	79.60	23.95	-	-
• Volume of urine (ml/24 h)	1512.33	215.34	1583.75	155.07	1595.00	189.22
• BUN (mg/dl)	11.22	2.27	11.40	2.87	15.60	6.89
• Plasma creatinine (mg/dl)	0.87	0.13	0.85	0.18	0.88	0.30
• Creatinine clearance (ml/min)	150.24	29.88	72.81 ^a	30.93	125.33	18.09
• Urine osmolality before						
8-h water deprivation (mosM/L)	720.00	33.30	368.0 ^b	199.43	607.40	208.12
• Urine osmolality after						
8-h water deprivation (mosM/L)	528.50	115.10	442.77	132.82	413.00	255.14
• Urine osmolality after						
Minirin injection (mosM/L)	688.86	120.66	586.55	160.44	650.42	151.63

a: Statistically lower than the other two groups (F=14.10, p<0.01)

b: Statistically lower than the other two groups (F=4.31, p<0.05)

All patients on Li treatment were taking multiple dosage of Li (b.i.d. or t.i.d.). None of the patients had a past history of renal disease, cardiovascular disorder, diabetes mellitus or any other systemic diseases. At the time of the study, all Li-treated patients were on Li alone and Li-naïve patients were drug-free at least for one week. The study protocol was approved by the ethics committee of our hospital, and the patients gave their written informed consents.

Renal functioning testing procedure

All subjects were hospitalised for 3 days in the psychiatric ward. The following analyses were done in all subjects: Serum BUN, creatinine and Li levels, urine creatinine levels, urine osmolality before and after 8 hour water deprivation and urine osmolality after desmopressin (Minirin) injection. In the morning of day 1, fasting blood samples were collected, centrifuged immediately, and frozen at -20°C until assay time for determination of serum BUN, creatinine and Li levels. Serum BUN and creatinine levels were measured by Ilab autoanalyser. Serum Li monitoring was performed by atomic absorption spectrophotometry.

Urine output was collected from 8:00 a.m. on day 1 until 8:00 a.m. on day 2, and its volume was measured. All urine samples were stored at $4-8^{\circ}\text{C}$, and creatinine levels were determined in 24 h urine collections. Creatinine clearance was calculated by using the following formula:

Urine creatinine (mg/dl) X 24 hour urine volume (ml)

Serum creatinine (mg/dl) X 1440 (min)

Determination of urine osmolality both before and after 8-h water deprivation and after desmopressin (ADH, Minirin 2mg) injection was carried out as renal concentrating ability test. Serum and urine osmolalities were determined by a Wescor automatic osmometer and expressed as mosM/L.

Water deprivation test was performed on the second day with the same protocol as described by Dash et al (1963) previously (12):

Test was performed under direct observation. Patients were not allowed to consume any fluid or food for 8 hours from 08:00 a.m. All patients were weighed basally and 97% of this weight was calcu-

lated. Afterwards patients were weighed at 4th, 6th, 7th and 8th hours. Plasma osmolality was measured urgently if the patient lost more than 3% of body weight, and if it was above 305 mosmol/kg, desmopressin was given and the patient was allowed to drink.

Water deprivation was continued for another hour if urine output had not decreased and/or urine: plasma ratio was less than 2.0 but the plasma osmolality had not become concentrated (>295 mosmol/kg). Desmopressin (Minirin, $2\text{ }\mu\text{g}$ i.m.) was administered at the end of the water deprivation period. Subsequently urine samples were collected hourly for another 4 hours but the patients were allowed to drink.

All urine volumes passed during the test were measured and recorded. Plasma samples were collected halfway through the relevant urine collection period.

Interpretation of the water deprivation test

Water deprivation test was interpreted as described by Baylis et al (1995) previously (13). Hypothalamic diabetes insipidus was diagnosed when urine osmolality was less than 300 mosmol/kg after fluid deprivation and higher than 750 mosmol/kg after desmopressin. Nephrogenic diabetes insipidus was diagnosed when urine osmolality was less than 300 mosmol/kg after fluid deprivation and after desmopressin. Patients whose urine osmolalities were higher than 750 mosmol/kg after fluid deprivation and after desmopressin were considered to be normal. Finally patients whose urine osmolalities were between 300 to 750 mosmol/kg after fluid deprivation but less than 750 mosmol/kg following desmopressin administration were considered to have partial nephrogenic diabetes insipidus.

Data analysis

Comparisons of the ages and renal values of the three groups were carried out with one-way ANOVA (post hoc Bonferroni's test). Serum Li levels of the short- and long-term Li groups were compared with Mann-Whitney U test.

Results

Table 1 shows the demographic and clinical vari-

ables of the patients, and the indices of renal function in the groups studied. The ages of the groups were not statistically different from each other ($F=0.89$, $df=2,29$, $p>0.05$). Serum Li levels were 0.71 ± 0.10 mmol/L in the short-term Li-treated group and 0.68 ± 0.20 in the long-term Li-treated group and no significant difference was found between them ($U=39.50$, $p>0.05$).

Serum BUN and creatinine levels were within the normal limits and not statistically different among the groups ($F=2.87$, $df=2,29$, $p>0.05$; and $F=0.05$, $df=2,29$, $p>0.05$, respectively). But the finding that creatinine clearance of the long-term Li-treated group was significantly lower than both that of the Li-naïve group and that of the short-term Li-treated group ($F=14.10$, $df=2,29$, $p<0.01$) indicated decreased GFR in the long-term Li-treated patients. Urine osmolality measured before 8-h water deprivation of the long-term Li-treated group was significantly lower than both that of the Li-naïve group and that of the short-term Li-treated group ($F=4.31$, $df=2,29$, $p<0.05$). However, when renal concentrating ability test was performed, after 8-h water deprivation and also after desmopressin injection, no differences were found among the groups ($F=0.42$, $df=2,29$, $p>0.05$; $F=0.95$, $df=2,29$, $p>0.05$). When each patient was evaluated individually in terms of their renal concentrating ability, partial nephrogenic diabetes insipidus was diagnosed in 4 patients on long-term and in 2 patients on short-term Li-treatment. Hypothalamic diabetes insipidus was also diagnosed in other 2 patients on long-term Li-treatment. Renal concentrating ability was relatively normal in Li-naïve bipolar patients. Taking into consideration all the patients treated with Li, no significant correlation was found between the serum Li level or the duration of Li therapy and any of the renal functioning ability variables.

Discussion

In this study, we found that 8 of the 20 patients on Li treatment had reduced renal concentrating ability. Just 2 of them were on short-term Li treatment but the others were on long-term Li treatment lasting up to 10 years, while Li-naïve bipolar patients did not have such a degree of renal functioning abnormality as expected. Our results demonstrate that all of the patients having a deficit in renal concentrating ability did not have ADH-resistant impair-

ment of renal-concentrating ability. Therefore, they were diagnosed to have partial nephrogenic diabetes insipidus. But surprisingly, 2 of 10 long-term Li-treated patients were diagnosed to have hypothalamic diabetes insipidus. This result is in concordant with that of Martines-Maldonado et al (1975) who reported that renal concentrating deficit occurring in Li-administered rats would be with mixed renal and hypothalamic origin (11), although most of the previous studies reported that Li-induced impairment in renal concentrating ability resulted from a resistance of the collecting ducts to ADH (2,3,9). In line with our result, it has also been reported in some animal studies that Li can cause hypothalamic diabetes insipidus by leading to increase gene expression of ADH in paraventricular (PVN) and supraoptic (SON) nuclei of hypothalamus (14). Altogether, it can be considered that Li-induced diabetes insipidus may originate not only from the resistance of the renal tubuli to ADH, but also from suppression of the secretion of ADH on the hypothalamic level in some cases.

We found creatinine clearance to be significantly lower in the long-term Li treated group than in both the Li-naïve and short-term Li-treated groups. This result indicates that long-term Li treatment may lead to a decrease in GFR and a tubular damage supporting some previous studies (2,3). However, there are also some studies reporting that both glomerular and tubular functions were unimpaired and renal concentrating ability was fully preserved with long-term Li treatment (8,15,16). Povlsen et al (1992) reported no significant impairment of renal function following Li treatment in their prospective study lasting up to 10 years (16). Although Lokkegaard et al (1985) reported that decrease in GFR is detectable only after many years of Li treatment (4), most investigators have found no clinically significant effect on the GFR (6,8,16,17). Therefore, we can say that our result of decreased GFR in long-term Li treated patients is not in agreement with that of most previous studies.

These conflicting results can be explained by the duration of Li treatment, patients' age, patients' gender or pre-lithium renal conditions of patients and also different Li dosage and single or multiple dosages given. Li-induced impairment in renal concentrating ability has been reported to be associated with a longer duration of Li treatment, which is in consistent with our results, and higher plasma Li lev-

els (6), or a multiple daily dosing schedule (7,8). It has also been reported that increased female sensitivity to Li in terms of renal side effects (8,18). Furthermore, the impairment of concentrating capacity may not be specifically related to Li, but also to other factors associated with mood disorder. Controlled studies have shown that renal concentrating capacity was impaired both in Li and non-lithium-treated bipolar patients, but the difference was not significant, and all groups had mean values below 800 mosmol/kg H₂O (18). Although our study lacked a healthy control group, the fact that our Li-naïve bipolar patients had mean values 607 mosmol/kg H₂O may support this idea.

Some studies suggest that renal functioning and

structure are less affected in organisms receiving Li once a day compared with patients given Li divided daily doses (7,8,19). The fact that our patients have been given Li in divided daily doses may partly explain the renal damage found.

In conclusion, this study demonstrates that long-term Li treatment may cause an impairment in renal concentrating ability some of which may originate from the effects of Li on hypothalamic level, and a decrease in GFR. In the light of these data, we can conclude that the duration of Li treatment is one of the main determinants of Li-induced renal changes in bipolar patients. However, it may be argued that our sample is quite small and lack pre-treatment (baseline) data of the Li-treated patients.

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