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Winter Sale on Lithium Levels: The Impact of Seasonality

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ÖZET:

Lityum düzeylerinde kış indirimi: Mevsimsel döngüselliğin önemi

Amaç: Lityum duygudurum bozukluklarının koruma tedavisinde etkili bir ilaç olarak tüm dünyada tanınmaktadır. Lityumun bipolar bozukluk profilaksisindeki etkinliği yetmişli yılların başından beri kanıtlanmıştır. Lityum bipolar bozuklukta akut duygudurum epizodları farmakoterapisi, döngülerin önlenmesi, önleyici tedavi ve intiharın önlenmesinde dayanak noktası olmuş ve olmaya devam etmektedir. Bazı ülkelerde lityum düzeylerinin mevsimsel değişiklikleri olduğu şeklinde yayınlar mevcuttur. Mevsimsel değişme ile ilişkili olarak lityum düzeyindeki değişiklikler klinik etkinliğin olmamasına ya da toksisiteye yol açabilir. Bipolar bozukluk hastalarında yaz ve kış mevsimleri arasında lityum düzeylerini karşılaştırmayı amaçladık.

Yöntem: Bakırköy Psikiyatri Nöroloji ve Nöroşirurji Eğitim ve Araştırma Hastanesi Raşit Tahsin Duygudurum Kliniğince izlenen ötimik bipolar bozukluk hastaları çalışmaya alındı ve lityum düzeyleri kış ve yaz mevsimlerinin ikinci yarısında (15 Haziran - 1 Eylül ve 15 Ocak - 1 Mart arası) lityum düzeyleri ölçüldü. 32 Bipolar bozukluk hastası için plazma lityum düzeyi, yaş ve cinsiyeti kapsayan bir yıllık süreyi içeren ileriye dönük olgu gözlem dosyası hazırlandı. İzlem süresince herhangi bir sebeple lityum tedavi dozu değişen bipolar bozukluk hastaları çalışmadan çıkarıldı. Bipolar bozukluk tedavisi dışında lityum kullanan hastalar çalışma dışı bırakıldı. Zeka geriliği, madde bağımlılığı, lityum tedavisinin kontrendike olduğu (kalp hastalığı, böbrek hastalığı, epilepsi, Parkinson hastalığı gibi) hastalıklar düşük plazma lityum düzeyine yol açıp, tedaviye uyum sorunu oluşturabilecekleri için çalışma dışı bırakıldı. Antihipertansif ilaçlar, nonsteroidal antienflamatuar ilaçlar, bazı antibiyotikler, topiramat ve diüretikler plazma lityum konsantrasyonunu arttırabilecekleri için ve teofilin lityum konsantrasyonunu azaltabileceği için, bunların kullanımı dışlama ölçütü olarak kabul edildi. Sodyum düzeyleri de lityum düzeyleri üzerine olası etkileri sebebiyle izlendi. Lityum kan düzeyleri eşleştirilmiş grupların t testi ile karşılaştırılmış, lityum düzeyini etkileyebilecek parametreler için bağıntı analizi yapılmıştır.

Bulgular: Hastaların yaş ortalaması 35.75±9.59, hastalığın başlangıç yaşı ortalaması 21.97±6.17, ortalama hastalık süresi 13.90±9.41 olarak tespit edildi. 32 hastanın 15'i erkek cinsiyetteydi. Hastalar tarafından kullanılan ortalama lityum dozu 1190.6±249.0 mg/gün olarak bulundu. Plazma lityum düzeyi ortalaması kış mevsiminde 0.75±0.12 mEq/L, yaz mevsiminde 0.83±0.12 mEq/L olarak tespit edildi (p=.003). Serum sodyum düzeyleri yaz aylarında 139.1±2.2 mEq/L ve kış aylarında 137.1±2.3 mEq/L olarak belirlendi (p=.001). Lityum ve sodyum düzeyleri arasındaki ilişki yaz ve kış mevsimlerinde belirgin değildi (sırasıyla p=0.55, r=0.12 ve p=0.49, r=0.14).

Sonuç: Bu çalışma yaz ve kış mevsimleri karşılaştırıldığında lityum düzeylerinde belirgin değişiklik olduğunu göstermektedir bu yüzden bipolar bozukluk hastalarında sık plazma düzeyi ölçümü ve lityum doz ayarlaması toksisite ve etkinlik azalması durumlarını önleyebilir. Lityum düzeyleri yaz mevsiminde dehidratasyon dolayısı ile göreceli olarak artabilir. Mevsimselliğin bipolar bozukluk ya da diğer bozukluklar üzerine özgünlüğünü ayırt etmek için ileriye dönük kontrollü çalışmalara ihtiyaç bulunmaktadır.

Anahtar sözcükler: lityum, bipolar bozukluk, mevsimsel değişiklik, terapötik ilaç düzeyi

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ABSTRACT:

Winter sale on lithium levels: the impact of seasonality

Objective: Lithium is recognized worldwide as an effective prophylactic agent in mood disorders. Prophylactic efficacy of lithium in mood disorders has been established since the early seventies. Lithium has been and continues to be the mainstay of bipolar disorder (BD) pharmacotherapy for acute mood episodes, switch prevention, and suicide prevention. There are reports of seasonal variation in lithium levels from a few countries. Variability in the lithium level can lead to a lack of efficacy or to toxicity, making seasonal variation clinically relevant. We aimed to compare lithium levels of bipolar patients between summer and winter.

Methods: Euthymic bipolar patients who were followed in the Raşit Tahsin Mood Clinic of the Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery were recruited for the study, and lithium levels were measured in the second part of winter and summer (15th of June to 1st of September and 15th of January to 1st of March). A prospective case sheet audit was performed for 32 BD patients for recording plasma lithium level, age and gender for one year. Bipolar patients whose treatment dosage of lithium was changed for any reason during the study follow-up were excluded. Situations of lithium use other than for bipolar disorder were excluded. The presence of concomitant diagnoses of mental retardation or drug dependence constituted exclusion criteria, as did medication non-compliance detected by persistently low lithium plasma levels. The use of antihypertensive drugs, nonsteroidal anti-inflammatory drugs, theophylline, some antibiotics, topiramate, and diuretics that could cause an increase in plasma concentrations of lithium, and of theophylline that could reduce lithium concentrations constituted exclusion criteria. Sodium levels were also monitored due to their propable effect on lithium levels. Lithium levels were compared using the paired sample t-test. Correlation analysis was done for the parameters that could affect lithium levels.

Results: The mean age of the patients was 35.75±9.59 years, the mean age of onset was 21.97±6.17 and the mean duration of disorder was 13.90±9.41 year. 15 out of 32 patients were male. The overall average dose of lithium taken by the patients was 1190.6±249.0 mg/day. The mean lithium plasma level was 0.75±0.12 mEq/L in winter, and the mean lithium plasma level was 0.83±0.12 mEq/L in summer (p=0.003). The overall serum sodium levels were 139.1±2.2 mEq/L in summer and 137.1±2.3 mEq/L in winter (p=0.001). The correlation between lithium and sodium levels was not significant in summer or in winter (respectively p=0.55, r=0.12 and p=0.49, r=0.14).

Conclusions: The present study showed a significant variability of lithium levels when comparing summer and winter. Therefore, frequent plasma level monitoring and oral lithium dose adjustment to prevent situations of toxicity or lack of efficacy in bipolar disorder are suggested. Lithium levels may show a relative increase in summer due to dehydration. Prospective controlled studies are required to differentiate whether this seasonality is specific to bipolar disorders or not.

Keywords: lithium, bipolar disorder, seasonal variation, therapeutic medicine level

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INTRODUCTION

Lithium is an important drug in the treatment of bipolar disorder (BD), being effective both for the treatment of acute mania and for prophylaxis (1). The lithium ion is rapidly absorbed by the intestinal mucosal membrane and is eliminated almost exclusively by the kidneys.

Lithium's therapeutic window is between 0.6 and 1.2 meq/L serum levels. Serum levels of lithium above the maximal limit produce intoxication (2). Changes in plasma levels seem to increase the risk of relapse (3). Lithium levels must be monitored carefully during follow-up due to its narrow therapeutic index. (4). Drugs that alter renal function can increase the risk for chronic lithium toxicity (5,6). Anorexia, cystic fibrosis, decreased effective circulating volume (eg. cirrhosis, congestive heart failure, nephrotic syndrome), decreased dietary sodium intake, diabetes insipidus, diabetes mellitus, gastroenteritis, infections, medications (e.g. angiotensin-converting enzyme inhibitors, cyclosporine, diuretics: loop diuretics and thiazides, nonsteroidal anti-inflammatory drugs, tetracycline), overdose, renal insufficiency, schizophrenia, surgery and volume depletion are the factors that increase the risk for chronic toxicity in previously stable patients (5,7,8).

Several studies have indicated that low blood levels are associated with a greater risk of relapse (9-11). Moreover, changes in blood lithium levels have been observed to occur in some patients on a constant lithium dose, in association with major shifts in mood state (12).

Seasonal variation in the incidence of bipolar disorder, suicide, mania and depression have been observed and a potential relation to temperature variation has been suggested (13-16). There are conflicting observations regarding the response of psychiatric illnesses to lithium in different seasons (17,18). The observations show lower lithium plasma levels in autumn, a finding that could be linked to a peak of depressive relapses that occurs in that season, but not in spring (19).

Seasonal variation in lithium levels have been reported in the literature from India, Italy, the Netherlands and the United States (20-22).

Considering the impact of seasons on the course of illness in bipolar disorders, cautious monitoring of lithium levels becomes more important. With this backgound, in this study we aimed to compare lithium levels of bipolar patients between summer and winter.

METHODS

Euthymic bipolar patients who were followed in the Raşit Tahsin Mood Clinic of the Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery were recruited for the study, and lithium levels were measured in the second part of winter and summer (15th of June to 1st of September and 15th of January to 1st of March). The diagnoses of the patients were confirmed by two seperate psychiatrists according to the Structural Clinical Intervew for the DSM-IV. Bipolar patients whose treatment dosage of lithium was changed for any reason during the study follow-up were excluded.

Situations of lithium use for diagnoses other than BD were excluded. The presence of concomitant diagnoses of mental retardation, drug dependence, or contraindicated lithium therapy (e.g. heart disease, kidney disease, epilepsy, Parkinsonism) constituted exclusion criteria, as did medication non-compliance detected by persistently low lithium plasma levels. The use of anti-hypertensive drugs like angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, theophylline, some antibiotics (metronidazole, levofloxacin, trimethoprim/ sulfamethoxazole), topiramate, and diuretics that can cause an increase in plasma concentrations of lithium, and theophylline, which could reduce lithium concentrations, constituted exclusion criteria.

We measured plasma levels of lithium in 32 subjects affected by bipolar disorder (n=17, females, 53.1%; n=15, males, 46.9%) between 19 and 60 years of age. Missing data for sodium or lithium levels at any visit was not included in the

statistical analysis. Thus, the number of patients indicated in the tables was lower than the total sample.

All patients received lithium as maintenance therapy with doses adjusted to obtain 12-h plasma levels within the standard therapeutic range of 0.6–1.2 mEq//l, and then the dose remained unchanged. Sodium levels were also monitored due to its probable effect on lithium levels. All data were analysed using the Statistical Packages for the Social Sciences (SPSS) version 16 and lithium levels were compared using the paired sample t-test. Pearson correlation analysis was done for the parameters that could affect lithium levels.

RESULTS

Data from 32 patients was collected. 15 (46.9%) were males, 17 (53.1%) were females and the mean age was 35.75±9.59 years. The overall average dose of lithium taken by the patients was 1190.6±249.0 mg/day.

The mean age of onset was 21.97±6.17, and the mean duration of disorder was 13.90±9.41 years. 31.2% (n=10) of patients were treated with 900mg/day, 43.8% (n=14) of patients were treated with 1200 mg/day, 21.9% (n=7) of patients were treated with 1500 mg/day, and 3.1% (n=1) of patients were treated with 1800 mg/day.

We observed a significant difference in lithium plasma levels across seasons in the whole sample, with higher levels in summer than in winter (p=0.003). The overall mean lithium plasma value was 0.83±0.12 mEq/L in summer and 0.75±0.12 mEq/L in winter. The overall serum sodium levels were 139.1±2.2 mEq/L in summer and 137.1±2.3 mEq/L in winter. We observed a significant difference in serum sodium levels across seasons in the whole sample with higher levels in summer than in winter (p=0.001) (Table 1). However, the correlation of lithium and sodium levels was not significant in summer or in winter, respectively (p=0.55, r=0.12 and p=0.49, r=0.14) (Table 2).

Table 1: Seasonal variation of lithium and sodium concentration

Summer and winter concentration	n#	mean± SD	t	P
Plasma Lithium summer-winter	27	0.83±0.12-0.75± 0.12	3.3	0.002
Serum Sodium summer-winter	30	139.1±2.2-137.1±2.3	4.8	<0.001

#missing data were not included

Table 2: Correlation of lithium and sodium levels

Seasonal correlation of lithium and sodium levels	n#	Pearson	p
Lithium-sodium (summer)	27	0.12	0.55*
Lithium-sodium (winter)	26	0.14	0.49*

*p>0.05 statistically nonsignificant, #missing data were not included

DISCUSSION

Lithium is the lightest alkali metal and a monovalent cation, and it shares some properties with sodium, potassium, and calcium (23,24). Substitution or competition with other cations may contribute to its effects and many other factors may influence lithium levels (24).

Studies done in Italy, the Netherlands, the United States and India have shown higher lithium levels in summer (20-22). Perspiration leading to loss of sodium and water from the skin, resulting in a compensatory increased reabsorption of monovalent cations like lithium from the nephrons, is suggested to cause this increased level (21). It has been previously reported that lithium levels can be affected by seasons and temperature (25). In line with this literature, in our study lithium levels were found to be higher in summer without a correlation with sodium levels.

Additionally, some of pharmacological agents may increase lithium levels. In the manic phase, phenothiazines, which increase erythrocyte lithium concentrations and renal clearance of lithium should be avoided, in favor of haloperidol, which is reported to have a moderate and mostly pharmacodynamic interaction (26). Our sample group consisted of euthymic bipolar patients who did not use phenothiazines. Therefore, the seasonal variation in serum lithium levels can be interpreted to be independent of drug interactions.

On the other hand, there are conflicting observations regarding the response of psychiatric illnesses to lithium in different seasons (17,18). In addition, perspiration leading to loss of sodium and water from the skin, resulting in a compensatory increased reabsorption of monovalent cations like lithium from the nephrons, is suggested to cause this increased level (21). The same authors reported a significant elevation of lithium plasma levels in summer with a more marked variation among early-onset subjects, bipolar subtype, and females (21), and one study reported that men maintained on lithium showed higher levels of lithium in serum during the summer (20). Beersma et al. evaluated lithium levels in the four seasons and reported that serum lithium levels were 0.706±0.112 mmol/l in autumn, 0.718±0.105 mmol/l in winter, 0.740±0.125 mmol/l in spring, and 0.744±0.116 mmol/l in summer (18).

For this reason, seasonal changes of lithium levels as determined in our study is even more important especially in patients of bipolar disorder with seasonality. This seasonal change in the levels of lithium may be associated with unresponsiveness to lithium treatment and/or recurrence of the disease.

Lithium may influence transepithelial electrolyte movement through a partial substitution of lithium for other ions, especially sodium and potassium (27). There is an intricate electrolytic equilibrium between sodium and/or water and lithium (28). Lithium can substitute for sodium or potassium on several transport proteins that normally transport sodium or potassium, thus providing a pathway for lithium entry into cells. The pathways for transporting lithium out of cells are more limited, resulting in lithium accumulating intracellularly (29). Sodium-lithium countertransport (Na-Li CT) is a membrane transport system involving a one-to-one exchange of sodium for lithium, usually measured as sodium-dependent lithium efflux in lithium-loaded red blood cells (RBCs). Na-Li CT affinity for lithium is approximately 15- to 18-fold greater than that for sodium (30,31). Patients treated with lithium for a bipolar disorder typically have serum sodium and lithium concentrations of approximately 140 mEq/L and 0.6 to 1.5 mEq/L, respectively (30,31).

In our study, the fact that the lithium and sodium plasma levels were not correlated, suggests that the season affects the level of lithium through other possible mechanisms.

Our study has several limitations; firstly, it was performed in specialized centers that may be biased by restrictive selection criteria (32); therefore, we cannot exclude a potential bias associated with severity. Evaluation of lithium levels only in two seasons and with a relatively small sample size were the other limitations of our study.

CONCLUSIONS

Frequent drug level monitoring and oral dose adjustment of lithium are required to avoid significant variation in plasma lithium levels that can otherwise lead to toxicity or lack of efficacy due to its narrow therapeutic index. Thus, in light of the literature and our findings, we think that seasonality of lithium levels must be kept in mind for mood episodes and prophylaxis of bipolar disorders. Lithium levels may increase relatively because of dehydration in summer. Prospective controlled studies are required to differentiate whether this seasonality is specific to bipolar disorders or not.

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