Effects of Lithium Treatment on Granulocytes and Granulocyte Colony-Stimulating Factor in Patients with Bipolar Affective Disorder*

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ABSTRACT:
EFFECTS OF LITHIUM TREATMENT ON GRANULOCYTES AND GRANULOCYTE COLONY-STIMULATING FACTOR IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER

Objective: Although there are conflicting results, lithium carbonate has been demonstrated to induce the production of haematopoietic cells, particularly white blood cell series. In this study, we examined the effects of lithium on white blood cells in association with granulocyte colony-stimulating factor (G-CSF), which is a polypeptide growth factor that regulates the production of neutrophilic granulocytes. **Methods:** Eighteen lithium-naive (8 females, 10 males; mean±SD age: 36±7.9 years) and 20 long-term lithium treated (9 females, 11 males; mean±SD age: 37.4±9.5 years) bipolar patients were included in the study. In the lithium-naive patients, lithium treatment was started to provide prophylactic serum lithium concentrations after blood samples were taken to determine the baseline haematological values (white blood cell, granulocyte and lymphocyte counts, haematocrit and G-CSF concentration). Blood samples were reobtained in the first and fourth weeks in this group. The same measurements were fulfilled once in the patients on the long-term lithium treatment. **Results:** The values of granulocyte count were significantly increased in the fourth week of lithium administration compared to the baseline values in the patients who were in the short-term lithium treatment, and this increase was associated with some elevation of G-CSF values that did not reach significance. The values of granulocyte count in the long-term lithium group were not significantly different from those of the baseline values of lithium-naive patients. **Conclusion:** Granulocytosis induced by lithium treatment in bipolar patients cannot be explained solely by the stimulation of G-CSF activity. Increased granulocyte count seems to approach the baseline values during the long-term lithium treatment.

Key words: lithium, granulocyte, white blood cells, granulocyte colony-stimulating factor, bipolar affective disorder.

Bull Clin Psychopharmacol 2001;11:28-32

ÖZET:
BİPOLAR AFFEKTİF BOZUKLUKLU HASTALARDA LİTYUM TEDAVİSİNİN GRANÜLOSİTLER VE GRANÜLOSİT KOLONİ UYARICI FAKTÖR ÜZERİNE ETKİSİ

Amaç: Tartışmalı sonuçlar olsa da, lityum karbonatın hematopoetik hücreler ve özellikle beyaz kan hücrelerinin üretimini artırdığı bildirilmiştir. Bu çalışmada lityumun beyaz küre hücreleri ve nötrofilik granülositlerin üretimini düzenleyen bir polipeptid büyüme faktörü olan granülosit koloni uyarıcı faktör (G-CSF) üzerine etkileri araştırıldı. **Yöntem:** Çalışmaya henüz hiç lityum kullanmamış 18 (8 kadın, 10 erkek; yaş ortalaması: 36±7.9) ve uzun süredir lityum kullanmakta olan 20 (9 kadın, 11 erkek; yaş ortalaması: 37.4±9.5) bipolar hasta alındı. İlk gruptaki hastalardan lityum başlanmadan önce ve başlandıktan sonraki 1. ve 4. haftalarda hematolojik değerleri (beyaz küre, granülosit ve lenfosit sayıları, hematokrit ve G-CSF değerleri) tespit etmek üzere üç kez kan alındı. Uzun süreli lityum grubunda aynı ölçümler bir kez yapıldı. **Bulgular:** Kısa süreli lityum grubunda lityum başlanmasının 4. haftasındaki granülosit sayısı bazal değerlere oranla anlamlı biçimde artmış bulundu, ve bu artış G-CSF değerlerinde anlamlılık düzeyine ulaşmayan bir miktar artışla birlikteydi. Uzun süreli lityum grubundaki granülosit sayısı ise henüz lityum başlanmamış hastaların bazal değerlerinden farklı bulunmadı. **Sonuç:** Bipolar hastalarda lityum tedavisinin yol açtığı granülositozis yalnızca G-CSF aktivitesinin uyarılmasıyla açıklanamaz. Lityum tedavisine bağlı olarak artan granülosit sayısı uzun süreli tedavi boyunca normale dönüyor gibi görünmektedir.

Anahtar sözcükler: lityum, granülosit, beyaz küre hücreleri, granülosit koloni uyarıcı faktör, bipolar affektif bozukluk.

Klinik Psikofarmokoloji Bülteni 2001;11:28-32

INTRODUCTION

Lithium carbonate, a drug used for prophylacsis of bipolar affective disorder, is capable of influencing many aspects of blood cell production, in particular, granulocytes (1,2,3,4). However, conflicting results have been obtained from clinical studies so far. We previously reported that lithium-

*Bu çalışma 13-17 Eylül 1997'de Avusturya- Viyana'da yapılan "10. European College of Neuropsychopharmacology (ECNP)" kongresinde bildiri olarak sunulmuştur.

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induced granulocytosis might be transient despite the continuation of long-term lithium therapy in patients with bipolar affective disorder (5). Haemapoietic cell proliferation, differentiation and renewal appear to be regulated by a large number of cytokines designated as colony-stimulating factors (CSF) or interleukins (IL) (6,7). Granulocyte colony-stimulating factor (G-CSF) is a polypeptide growth factor that regulates the production of neutrophilic granulocytes and acts on a relatively mature progenitor cell population that is primarily committed to neutrophilic differentiation (8). It is also a factor used to stimulate neutrophil production after chemotherapy and in other syndromes accompanying neutropenia (9). In this study, since lithium-induced haematological changes are primarily related to white blood cell series, we examined the effects of lithium on white blood cells in association with G-CSF in a similar patient population to our previous one (5).

MATERIAL AND METHOD

Subjects and Procedure

Eighteen lithium-naive outpatients (8 females, 10 males; mean±SD age: 36±7.9 years) who met DSM-IV criteria for bipolar I affective disorder (10) and who were candidates for lithium treatment were categorised as short-term (4 weeks) treatment group, and 20 bipolar outpatients (9 females, 11 males; mean±SD age: 37.4±9.5 years) who were in the long-term (more than 6 months) lithium treatment were categorised as long-term lithium treatment group (mean±SD duration of lithium treatment: 38.1±13.2 months). All patients were euthymic, non-rapid cycling and medication-free for at least 6 months except lithium carbonate. No patients had any neurological, metabolic, cardiologic, renal or endocrinologic disorders.

In the short-term treatment group, lithium carbonate treatment was started to provide prophylactic serum lithium concentrations after heparinised venous blood samples were taken to determine the baseline (before treatment) haematological values (haematocrit, red blood cell, white blood cell, granulocyte and lymphocyte counts, and plasma G-CSF concentration) and plasma basal cortisol levels. In order to minimise diurnal variations, all specimens were obtained at 08.00 a.m. Then, blood samples were obtained again in the first and fourth weeks of the lithium administration. Blood-samples were taken once in the patients who were on the long-term lithium treatment.

Haematocrit, white blood cell (WBC) and red blood cell (RBC) counts were measured by using standard Coulter counter technique (Coulter Electronics, MAX M Automated Haematology Analyser). Wright paint was used to prepare the peripheral blood smears. Separated sera were kept frozen at –20°C until analysed.

Plasma G-CSF concentration was measured in duplicate by Quantitative Enzyme Immunoassay (EIA) (Quantikine TM, R&D System Inc.) as described by Motojima et al. (1989) (11). The lowest sensitivity limit was 7.0 pg/ml. Absorbance measurement was read at 450 nm on Biotek ELISA reader.

Plasma cortisol levels were determined in duplicate by standard RIA (Amerlex, UK). The inter and intra-assay coefficients of variation were 7.9% and 7.0%, respectively. The lowest sensitivity limit of the method was 0.1 mg/100 ml and the normal range was 5.9 to 26.1 mg/100 ml.

Plasma and erythrocyte lithium concentrations were assessed by atomic absorption spectrophotometry and lithium values were expressed in milimole per litre (mmol/L) and in micromole per gram of haemoglobin (mmol/g Hb) for plasma and erythrocyte samples, respectively.

This study was approved by the local ethics committee and all subjects gave their written informed consent after full understanding of the study.

Statistical Analysis

Whether there is a difference in plasma and erythrocyte lithium levels between the short- and long-term groups was investigated by means of independent t-test. Comparisons of the haematological values of the baseline, first and fourth weeks of the short-term lithium group were performed by using paired t test. Two-tailed independent t test was used to compare haematological values of the long-term group with those of the short-term treatment group. The relationships between the haematological and clinical variables (age, duration of illness, duration of the use of lithium, erythrocyte and plasma lithium levels) were investigated by means of simple correlation-regression analysis.

RESULTS

Plasma lithium values in the fourth week of the short-term group (mean±SD: 0.72±0.13 mmol/l) were not different from those of the long-term group (mean±SD: 0.68±0.15 mmol/l) (t=0.84, p>0.5). Table 1 presents haematological variables of the two patient groups compared. We found that the values of granulocyte count significantly increased in the fourth week of lithium administration compared to the baseline and the first week's values in the patients who were in the short-term lithium group (t=2.87, p<0.05; t=2.79, p<0.05, respectively) (Table 1, Figure 1). Nevertheless, this increase was not associated with significant elevation in G-CSF concentrations, since we did not find any significant difference between the mean baseline G-CSF value and those in the first and fourth weeks (t=0.21, p>0.05; t=0.39, p>0.05, respectively). There was not any significant difference between G-CSF values in the first and fourth weeks, either (t=1.46, p>0.05). However, G-CSF values also tended to increase towards the first and fourth weeks of the lithium treatment, and to decrease in the long-term group although these tendencies did not reach statistical significance (Table 1, Figure 1). The values of the granulocyte count and plasma G-CSF in the patients who were on the long-term lithium treatment were not significantly different from those of the baseline, first and fourth weeks of the short-term lithium patients.

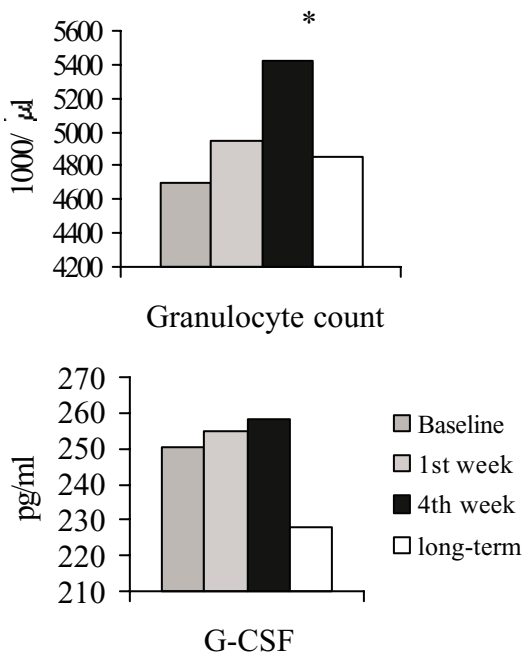

Figure 1. Baseline, first week, fourth week and long-term values of granulocyte count and G-CSF in the patients.

* Significantly different from those of the baseline and first week (t=2.87, p<0.05; t=2.79, p<0.05, respectively)

We found no correlations between any haematological and clinical variables, and between any of the haematological variables and cortisol values.

Table 1. Haematological and cortisol variables of the two patient groups

	Short-term Lithium Treatment Group (n=18)				**Long-term Lithium Treatment Group** (n=20)			
Laboratory variables	Baseline		1st week		4th week			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
WBC count (10^3/ml)	7284.0	1800.0	7707.6	2020.9	8118.1	2345.1	7591.6	1519.8
Granulocyte count (10^3/ml)	4697.3	531.2	4943.0	1479.4	5427.0*	1409.8	4850.0	1110.6
Lymphocyte count (10^3/ml)	1881.6	570.3	1844.3	722.3	1847.0	644.7	2258.3	463.1
Haematocrit (%)	43.8	3.5	42.3	5.3	42.7	4.7	41.3	5.0
G-CSF (pg/ml)	250.3	175.2	254.7	97.6	258.0	102.6	228.1	185.4
Cortisol (mg/dl)	26.3	6.2	18.1	7.9	27.5	11.3	21.2	5.9

* Significantly different from those of the baseline and first week (t=2.87, p<0.05; t=2.79, p<0.05, respectively)

DISCUSSION

It has been known that lithium can modulate granulopoiesis in concentrations of 0.3-5.0 mEq/l (2,12) via pluripotent stem cell stimulation and/or enhanced production of colony-stimulating factor, which is a haematopoietic hormone (13,14,15, 16,17,18). Lithium-induced leukocytosis and lymphopenia have been demonstrated with non-toxic therapeutic doses in humans (4,19,20,21,22) and animals (23). We observed that leukocytosis was not related to serum lithium levels or lithium concentrations within RBCs. This result is consistent with those of the majority of the above-mentioned previous reports.

In bone marrow, all haematopoietic cells originate from pluripotent stem cells (7). They are capable of self-renewal or of differentiation to a lymphoid cell (T or B lymphocyte) or give rise to a mature cell of the myeloid lineage such as an erythrocyte, neutrophil, monocyte/macrophage or platelet. The first step along the myeloid differentiation pathway results in a partially committed cell (colony-forming unit-granulocyte-erythroid-monocyte-macrophage or CFU-GEMM). This step requires granulocyte-macrophage-CSF (GM-CSF). CFU-GEMM further differentiates into granulocyte/ macrophage progenitor, erythroid progenitor or megacaryocyte progenitor cells (6). G-CSF and M-CSF act on the most differentiated colonies of granulocytes and monocyte/macrophages, respectively. The production of G-CSF is done by activated monocytes, fibroblast and endothelial cells. Different authors have reported that lithium has a positive induction on haematopoiesis and an increase in granulocyte/macrophage, erythroid and megakaryocyte progenitor cells (4,15,23).

Our finding that lithium-induced increase in granulocyte count in the 4th week of the lithium treatment was not associated with significantly increased G-CSF concentration suggests that this increase is not related to G-CSF stimulation by lithium. However, we observed an elevation to some degree parallel to the increase in granulocyte count in the fourth week, which did not reach significance. Induction of granulopoiesis by lithium can be at previous stages of granulocyte production probably through direct stimulation of pluripotent stem cells or myeloid progenitor cells, or enhanced sensitivity of myeloid progenitor cells to G-CSF (15,16,17,18). Furthermore, we found that granulocyte counts of the patients who were on long-term lithium treatment were not different from the baseline values of the short-term group. This result confirms our previous study indicating that significantly increased WBC count we observed on the 3rd day of lithium administration returned to baseline values with the long-term lithium treatment in the bipolar patients (5). Additionally, though not significant, the tendency to decrease in the G-CSF levels, which is parallel to the decrease in the granulocyte count in the long-term group, might be explained by a negative feedback in order to control the overproduction of granulocytes in the lithium-treated patients.

Corticosteroids are well known to elevate the leukocyte count during short- and long-term administrations (24) and there is some evidence for lithium stimulation of adrenocortical output of cortisol (20). In contrast to this idea, we did not find any significant correlation between cortisol values and leukocyte counts in the patients. This finding suggests that granulocytosis induced by lithium is due to direct effect on bone marrow of the drug, rather than via its effect on cortisol secretion.

In conclusion, granulocytosis induced by short-term lithium treatment in euthymic bipolar patients cannot be explained solely by the stimulation of G-CSF activity by lithium, and increased granulocyte count seems to approach baseline values during long-term lithium treatment in patients with bipolar affective disorder.

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