ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine 2013, Vol 20, No 1, 111-115
www.aaem.pl

Level of magnesium in patients with depression treated with lithium – pilotage research

Marta Makara-Studzińska[1], Wojciech Dąbrowski[2], Małgorzata Kiełczykowska[3], Irena Musik[3]

[1] *Independent Psychic Health Unit, Medical University, Lublin, Poland*
[2] *Department of Anaesthesiology and Intensive Therapy, Medical University, Lublin, Poland*
[3] *Chair and Department of Medical Chemistry, Medical University, Lublin, Poland*

Makara-Studzińska M, Dąbrowski W, Kiełczykowska M, Musik I. Level of magnesium in patients with depression treated with lithium – pilotage research. Ann Agric Environ Med. 2013; 20(1): 111-115.

Abstract

Introduction. Depression is a major public health problem. Magnesium (Mg^{2+}) is involved in many metabolic processes as an activator of over 300 different enzymes. For the last 60 years lithium (Li^{+}) compounds have been used in psychiatry. Li^{+} salts are regarded as the first choice medicine in the treatment of affective disorders and are also applied as an adjuvant intensifying the therapy in drug-resistant depression patients.

Objective. The objective of the study was an analysis of the relationship between the levels of magnesium, lithium, and education and place of residence of patients hospitalized due to depression.

Material and methods. Patients with bipolar affective disorders undergoing lithium therapy during their stay in the Department of Psychiatry at the Medical University in Lublin were examined. Patients were divided into three groups according to education level and were also analyzed according to place of residence.

Results. In the group of patients in the study, a significantly lower level of magnesium was found (p=0.02) in blood plasma of patients with secondary education level, compared to those who had elementary education. There was also a significantly higher level of magnesium (p=0.01) in blood plasma of patients who lived in urban areas, compared to rural inhabitants. No statistically significant differences were noted between lithium level in plasma, and the patients' place of residence (p=0.34).

Conclusion. Significantly higher plasma magnesium levels were observed among city than village inhabitants, there was also a relationship between type of education and magnesium level in blood plasma of the patients in the study. Further studies including larger groups of patients should be performed to enable a final conclusion.

Key words

depression, magnesium, lithium, education, place of residence

INTRODUCTION

Depression is a major public health problem [1]; however, to date, the pathogenesis of depressive disorders has not been clarified [1]. Research on the subject revealed relationships with disturbances of neurotransmission [2]. Serotonin and catecholamine neurotransmission have been found to be altered in depression [3, 4]. The results of studies suggest, however, that the pathogenesis of depression is more complicated [1], and that amino-acidergic transmission, as well as selected bioelements (e.g. zinc), can also play a role [5]. Some studies have also revealed that magnesium may affect NMDA receptor functions, as well as other systems involved in the pathophysiology of depression, which may suggest that this element is involved in the pathogenesis of the disease [6, 7].

Magnesium (Mg^{2+}) is the second most abundant intracellular cation and the fourth most abundant one overall in the human organism. As an activator of over 300 different enzymes it is involved in many metabolic processes. Mg^{2+} affects the nervous system through its actions on the release and metabolism of neurotransmitters and other mechanisms [8].

Address for correspondence: Marta Makara-Studzińska; Independent Psychic Health Unit, Medical University, Chodźki 15, 20-093 Lublin; Poland
E-mail: marta.makara-studzinska@umlub.pl

Received: 23 May 2012; accepted: 17 December 2012

The ability of magnesium to suppress hippocampal kindling, to decrease the release of adrenocorticotrophic hormone (ACTH), and to affect adrenocortical sensitivity to ACTH has been demonstrated [6]. The involvement of magnesium in the functioning of the central nervous system may be mediated via the N-methyl-D-aspartate-antagonistic, γ-aminobutyric acid agonistic, or the angiotensin II-antagonistic property of this ion [6, 9]. Magnesium also appears to have GABA(A)-agonistic or NMDA-antagonistic effects on sleep and nocturnal hormonal secretion, and hence it may exert a powerful effect on controlling the symptoms of depression and in preventing seizures [6, 10].

Furthermore, Mg^{2+} exerts a direct effect on the function of the transport protein P-gp (p-glycoprotein) at the level of the blood-brain barrier, possibly influencing the access of corticosteroids to the brain [6, 9]. Magnesium also dampens the calcium ion-dependent protein kinase related neurotransmission and stimulates the Na–K-ATPase. All these systems have been reported to be involved in the pathophysiology of depression [6]. Because of the importance of Mg^{2+} for monoamine neurotransmitter synthesis and receptor binding, it has behaviour-altering effects. The anti-depressant-like effect of magnesium is dependent on its interaction with the serotonergic, noradrenergic and dopaminergic receptors [9].

For the last 60 years, lithium (Li^{+}) compounds have been used in psychiatry [11]. Li^{+} salts are regarded as the first choice medication in the treatment of affective disorders [12] and

are also applied as an adjuvant intensifying the therapy in drug-resistant depression patients [13]. Interactions between lithium and magnesium have been described. Lithium and magnesium cations have similar physicochemical properties, and competition for binding sites in cellular components between these elements may be a part of Li^+ action [11, 14]. Studies on the mood-stabilizing influence of Li^+ have revealed that lithium may reverse some effects caused by magnesium [15]. Furthermore, lithium has been reported to influence homeostasis of both macro- and micro-elements [16, 17, 18].

The objective of the study was an analysis of the relationship between the levels of magnesium, lithium, and education and place of residence of patients hospitalized due to depression.

MATERIALS AND METHODS

Study protocol and patient distribution. The presented study was approved by the Committee for Bioethics at the Medical University in Lublin, and informed consents were obtained from all patients. Patients with bipolar affective disorders undergoing lithium therapy during their stay in the Department of Psychiatry at the Medical University in Lublin were examined. The criteria for enrolment of patients in the study were as follows: at least a two-year manic-depressive disorder of type I or II, current hospitalization due to a depressive episode without psychotic symptoms, absence of suicidal tendencies, no addiction to psychoactive substances, including benzodiazepines, no indication of the organic CNS injury, and aged over 18. Criteria for exclusion from the study were: pregnancy, breast-feeding, mental retardation, dementia, addiction to psychoactive substances, alcohol addiction, aged below 18, lack of consent to participate in the study, the presence of psychotic symptoms during the current hospitalization, concomitant chronic somatic disease. All of the patients enrolled in the study met criteria for a mild depressive episode of a moderate or severe degree without psychotic symptoms during the course of bipolar affective disorder according to the criteria for classification of mental and behavioral disorders.

On admission, all patients were prescribed lithium and the administered doses during the research in individual patients ranged from 500 mg-1,250 mg per day. Patients also received: sodium valproate at a dose of 800-1,500 mg/day, lamotrigine at a dose of 100-200 mg/day, carbamazepine at a dose of 600-800 mg/day, quetiapine at a dose of 250-400 mg/day, olanzapine at a dose of 10-20 mg/day and antidepressants: sertraline (50-100 mg/day), citalopram (20 mg/day), venlafaxine (150 mg/day).

None of the patients had ever received lithium treatment before the study. Evaluation of lithium and magnesium concentrations was made in the last (eighth) week of treatment.

Patients were divided into three groups according to education level: elementary, secondary, and university. Changes in Li^+ and Mg^{2+} were also analyzed according to place of residence – urban and rural. Venous blood samples (10 ml) were collected in heparin test tubes, and plasma was separated by centrifugation at 3,000 x g for 15 min. for measurement of magnesium and lithium. The obtained plasma was stored at the temperature of -20°C.

Mineral analysis. Total magnesium plasma concentrations were determined by the reaction with xylidyl blue (diagnostic set Liquick Cor-MG 60, manufacturer P.Z. CORMAY, Łomianki, Poland), using the colorimetric method. Wave length was 520 nm. The assays were carried out with the use of a SPECORD M40 (Zeiss Jena) spectrophotometer.

Lithium plasma concentrations were determined using ion-selective electrode Integrat 400 (Roche Diagnostics, Basle, Switzerland).

Statistical analysis. Mean and standard deviations (SD) were calculated for parametric data. Categorical variables were compared using the χ^2 and Fisher exact tests, and the Yates correction applied. The unpaired Student's t-test was used to analyse variables with a normal distribution. Non-parametric data were statistically analysed using the Wilcoxon signed-rank test and Kruskal–Wallis ANOVA test for initial detection of differences. $P < 0.05$ was considered to be statistically significant. The power of all statistical tests was determined by G*Power software ($1 - \beta$).

RESULTS

Sixty patients with bipolar affective disorder who were treated during the period from October 2010 – March 2011 were qualified for the study. A further 23 patients were excluded for the following reasons: withdrawal of consent to participate in the study, a suicidal attempt during hospitalization, discharge from the department upon request. Finally, 37 patients with bipolar affective disease were examined (Tab. 1), all of them were admitted to the Department of Psychiatry at the Medical University in Lublin due to an episode of depression, and hospitalized for 8 weeks. According to their education level, seven patients had basic (18.92%), 11 – secondary (29.73%) and 19 – university education (51.35%). According to place oe residence, 15 patients were from villages (40.54%), and 22 were from towns (59.46%).

Table 1. Characteristics of patients in the study

Characteristics of patients		Total
Education	Elementary	7 (18.92%)
	Secondary school	11 (29.73%)
	University	19 (51.35%)
Total		37 (100%)
Place or residence	Village	15 (40.54%)
	Town	22 (59.46%)
Total		37 (100%)

Plasma lithium concentrations were generally included into the recommended therapeutic range which was established as 0.6-1.0 mmol/l. In the group of patients in the study, a significantly lower level of magnesium was found (p=0.02) in blood plasma of patients with secondary education level, compared to those who had basic education. However, no statistically significant differences were noted between the magnesium level in blood plasma of patients who had university education, compared to those with basic and secondary education levels (p=0.23 and p=0.10, respectively) (Fig. 1). In addition, own studies showed a significantly higher level of magnesium (p=0.01) in blood plasma of patients

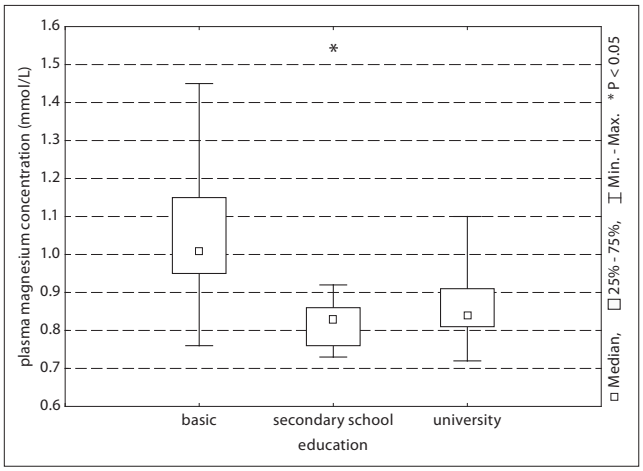

Figure 1. Changes in levels of magnesium in blood plasma according to education level

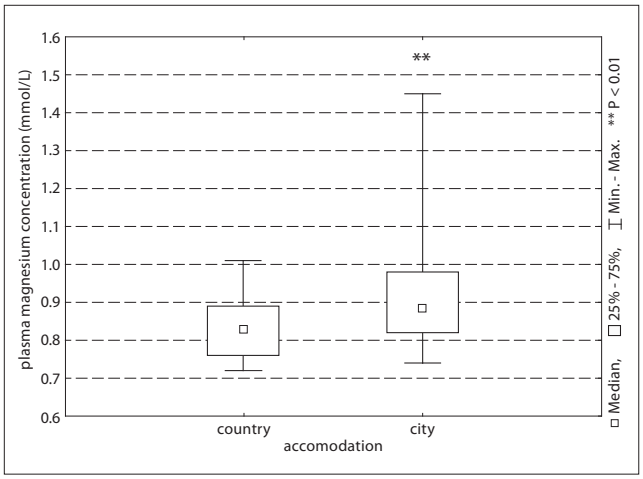

Figure 2. Changes in plasma magnesium levels according to place of residence

who lived in towns, compared to villages (Fig. 2). This may be due to the percentages of respondents with secondary and basic education level living in the country- 54% and 46%, respectively, whereas in the towns as many as 86% of patients possessed university education, while only 14% of respondents possessed secondary education. While analyzing the level of lithium in blood plasma of patients according to education, no statistically significant differences were

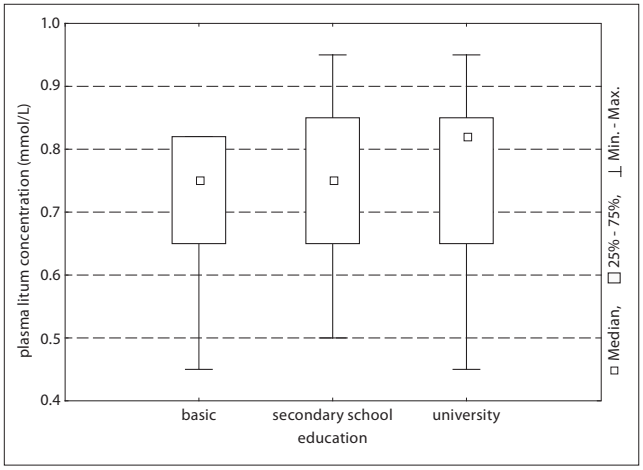

Figure 3. Changes in plasma lithium levels according to education level

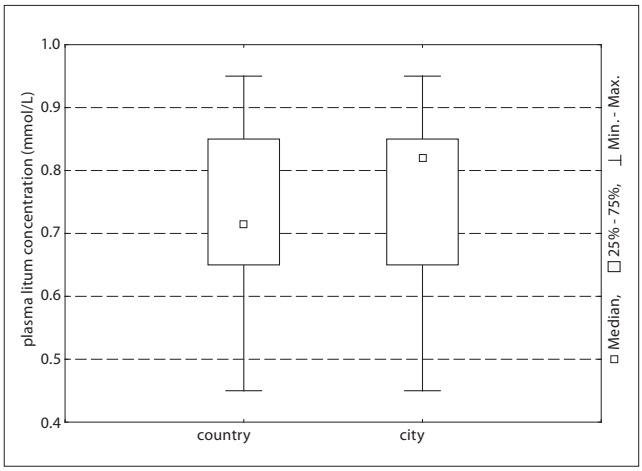

Figure 4. Changes in plasma lithium levels according to place of residence

found between respondents who had basic and secondary school education (p=0.72), and university education level (p=0.20), nor between respondents with secondary school and university education (p=0.58), (Fig. 3). No statistically significant differences were noted between lithium level in plasma, and the patients' place of residence (p=0.34) (Fig. 4).

DISCUSSION

Affective disorders afflict 10% of the population [19], characterized by alternate occurrences of depressive and manic episodes (affective bipolar disease), or solely depressive episodes (affective unipolar disorder). These are chronic and recurrent disorders associated with high premature death rates in relation with a high risk of committing a suicidal attempt, and a higher exposure to the development of somatic diseases, compared to the general population [20]. They also lead to serious consequences in the form of limitations in family and occupational functioning, and deterioration of the quality of life of the patients and their families.

Shealy et al. [21] confirmed that in almost all patients with depression there occurred a deficiency of magnesium and taurine. A hypothesis was developed that the majority of cases of major depression, including postpartum depression, may be associated with magnesium deficiency [8]. Reports have also been published concerning the magnesium level in cerebrospinal fluid in the course of depression. It has been confirmed [22] that both the level of 5-HIAA and magnesium in cerebrospinal fluid are decreased in individuals suffering from depression and suicidal thoughts. Magnesium ion neuronal deficits may be induced by stress hormones, an excessive supply of calcium, and deficit of magnesium in the diet. Dietary magnesium deficiency in combination with an excess of calcium and stress may cause other symptoms: excitation, anxiety, insomnia, headaches, delirium, hallucinations. A decrease in magnesium level is also observed in individuals with chronic fatigue syndrome and patients suffering from premenstrual tension syndrome – the disorders which may be related with a non-specific picture of depression [23, 24].

The results of the presented study show that the level of magnesium in blood plasma was significantly lower in patients with secondary school education than those who had basic education, and significantly lower among village than city dwellers.

Lithium is a medication of the first choice in the preventive treatment of bipolar affective disease. It is also used to enhance the treatment of drug resistant depression. The mechanism of action of the drug is not yet fully understood. Lithium influences the transportation of sodium via cellular membranes (sodium-potassium ATPase dependant) and has an inhibitory effect on a second (connected with phosphatidylinositol) transmitter system, probably acting in this manner as a stabiliser of inter cellular processes. Lithium does not bind with plasmatic proteins and is almost entirely excreted by the kidneys.

The side effects of the medication are related to its influence on the CNS, as well as the effect of lithium on renal transportation of electrolytes, and narrow therapeutic index of the medication. This may result in intoxication if medical recommendations are not adhered to [25, 26, 27, 28, 29, 30]. The most common side effects are: stomach aches, nausea, diarrhoea, lack of appetite, polydipsia, polyuria, trembling of hands, headaches, sleepiness, and deterioration of memory [19, 26, 27]. Lithium may cause weakening of the libido and erection disorders in males; however, this undesirable symptom of the therapy occurs rarely, and to-date it has not been explained to what extent it is affected by accompanying symptoms of depression [27, 31].

Pregnancy and the period of breastfeeding are absolute contraindications for beginning lithium treatment. The lithium ion penetrates through the placenta and in the plasma of the foetus reaches the same level as in the plasma of the mother [19, 32]. Pinelli et al. [32] carried out a review of reports from literature concerning the effect of lithium on the risk of prenatal complications. The following disorders most frequently occur in mothers treated with lithium: heart defects, primarily Ebstein's syndrome, cardiac arrhythmia, lower level of glucose in blood, reduced values of arterial pressure, respiratory failure, cyanosis, coma, thyroid function disorders, and hyperbilirubinemia. The majority of symptoms of the toxic effect of lithium on the foetus are transitory and exert no effect of further childhood [32].

Considering the indications and contraindications of lithium treatment and the occurrence of undesirable symptoms, the criteria for the enrolment of patients into own studies therefore did not cover: pregnancy, breastfeeding, mental retardation, dementia, addiction to psychoactive substances, alcohol addiction, lack of consent to participate in the study, presence of psychotic symptoms during the current hospitalization, concomitant chronic somatic disease.

While analyzing the level of lithium in blood plasma of patients according to education level and place of residence, no statistically significant differences were noted in the group of patients examined. However, further studies including larger groups of patients should be performed to enable a final conclusion.

CONCLUSIONS

1. Significantly higher levels of magnesium in blood plasma were observed among city than village dwellers.
2. A relationship was confirmed between the education level and level of magnesium in blood plasma of the patients examined. The lowest magnesium level was noted among patients with secondary school education.
3. No relationship was observed between the place of residence and the level of lithium in blood plasma in the group of patients in the study. The level of lithium in blood remained on a comparable level, irrespective of the patients' education.
4. Further studies including larger groups of patients should be performed to draw a final conclusion.

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