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REVIEW PAPERS

LITHIUM THERAPY – THE EFFECTIVENESS OF THE MEDICINE, SIDE SYMPTOMS, COMPLICATIONS AND THEIR INFLUENCE ON THE QUALITY OF THE LIFE IN AFFECTIVE DISEASES

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Abstract

Lithium is a medicine of the first choice in the preventive treatment of bipolar affective disorder. It is also used to enhance the treatment of drug resistant depression. How excatly this element acts is not yet fully understood. Lithium influences the transportation of sodium via cellular membranes (sodium-potassium ATPase dependant), has an inhibitory influence on the second transmitter system (connected with phosphatidylinositol), thus probably acting as a stabiliser of inter cellular processes. Lithium does not associate with plasmatic proteins and is almost entirely excreted by kidneys. The side effects of the medicine are linked to its influence on the central nervous system and on the renal transportation of electrolytes as well as the narrow therapeutic index of the medicine, which can cause intoxication if the recommended doses are not when medical recommendations are not observed. The undesirable effects are more intensive when the level of lithium in the blood plasma increases. Among the most common side effects are stomachaches, nausea, diarrhoea, lack of appetite, polydipsia, polyuria, shaking hands, headaches, sleepiness or deterioration of memory. Complications during lithium therapy listed in lite-

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rature are ataxia, dysarthria, nystagmus and extrapyramidal symptoms, but the most severe complication is lithium poisoning. Lithium can be applied for a long-term maintenance treatment, which limits recurrence of the disease and improves the patient's family, social and occupational life. The inferior quality of life among patients with affective disease can result from the disorder itself or can develop on the somatic grounds, appear due to abuse of tobacco or alcohol, or else be a side effect of other medicines taken by the patient. Good co-operation with the patient during the therapy can lessen the pronouncement of undesirable symptoms and complications of a lithium treatment, and this in turn can improve of the quality of the patient's life.

Key words: lithium therapy, affective diseases.

TERAPIA LITEM – SKUTECZNOŚĆ LEKU, OBJAWY UBOCZNE, POWIKŁANIA I ICH WPŁYW NA JAKOŚĆ ŻYCIA W CHOROBACH AFEKTYWNYCH

Abstrakt

Lit jest lekiem pierwszego rzutu w leczeniu profilaktycznym choroby afektywnej dwubiegunowej. Stosowany jest również w celu potencjalizacji leczenia w depresji lekoopornej. Mechanizm działania leku nie jest w pełni poznany. Lit wpływa na transport sodu przez błony komórkowe z udziałem ATP-azy sodowo-potasowej, ma działanie hamujące na układ drugiego przekaźnika związanego z fosfatydyloinozytolem, funkcjonując prawdopodobnie w ten sposób jako stabilizator procesów wewnatrzkomórkowych. Lit nie wiąże się z białkami osoczowymi i prawie całkowicie wydalany jest przez nerki. Objawy uboczne leku mają związek z jego oddziaływaniem na ośrodkowy układ nerwowy, wpływem litu na transport nerkowy elektrolitów oraz wąskim indeksem terapeutycznym leku, co w przypadku nieprzestrzegania zaleceń lekarskich może zagrażać intoksykacją. Nasilenie objawów niepożądanych wzrasta wraz z poziomem litu w surowicy krwi. Wśród najczęściej pojawiających się objawów ubocznych stosowania leku wymienia się bóle brzucha, nudności, biegunkę, brak łaknienia, polidypsję, poliurię, drżenie rąk, bóle głowy, senność, pogorszenie pamięci. Wymieniane w literaturze powikłania terapii litem to: ataksja, dyzartia, oczopląs i objawy pozapiramidowe, a najcięższe powikłanie to zatrucie litem. Lit daje możliwość długoterminowego leczenia podtrzymującego, ograniczającego nawroty choroby, co poprawia funkcjonowanie rodzinne, społeczne i zawodowe chorych. Gorsza jakość życia pacjentów z rozpoznaniem choroby afektywnej może wynikać z samego zaburzenia, przyczyn somatycznych, nadużywania używek, a także skutków ubocznych stosowanych leków. Dobra współpraca pacjenta w terapii wiąże się ze zmniejszeniem wystąpienia objawów niepożądanych i powikłań leczenia litem, przez co może wpływać na poprawę jakości życia pacjentów.

Słowa kluczowe: terapia litem, choroby afektywne.

INTRODUCTION

First attempts at using lithium for therapeutic purposes were made in the 1900s, but it was not until the second half of the 20th century that some clinical evidence for therapeutic effect of lithium in affective disorders was obtained, including the prophylaxis of bipolar affective disease recurrences, therapy of manic and depressive episodes and potentation of antidepressant action. Mood disorders affect 10% of the general population

(PUŻYŃSKI, BERĘSEWICZ 1993). In these disorders, there are alternately occuring depressive and manic episodes (bipolar affective disease) or depressive alone (unipolar affective disease). Mood disorders can be chronic and recurrent, and they are associated with high preterm mortality due to a high risk of suicidal attempts and increased exposure to somatic illnesses compared to the general population (PUŻYŃSKI 2002). Mood disorders have serious consequences, like the deteriorated quality of family and profesional life among patients and their families.

Lithium is a metallic element widespread in nature. In psychiatry, lithium is used in the form of easily dissociating salts, and the most common preparations are lithium carbonates and citrates. The therapeutic action is displayed by lithium cations, which are easily absorbed in the gastrointestinal tract after oral intake, are not bound by plasma proteins and are not metabolised so that almost all of the amount taken by the patient is excreted by the kidneys. The maximum blood concentration appears 2-4 hours after the intake (PUŻYŃSKI, BERĘSEWICZ 1993, RYBAKOWSKI 2003, SCHOU 2006).

THE AIM OF THE ARTICLE

This paper contains our analysis of the data available in the literature data concerning the efficacy of lithium, side effect occurring during lithium therapy and complications disturbing the course of the therapy and deteriorating the quality of life of patients with bipolar or unipolar affective disease.

MECHANISM OF LITHIUM ACTION AND ITS EFFECTIVENESS

The complex mechanism of lithium ionic action at the cellular level is not yet fully understood. There are reports about lithium regulating transportation of sodium via cellular membranes with the help of sodium-potassium adenosine-5'-phosphatase. Lithium modifies intracellular transmission through its effect on the second transmitter system: phosphatidylinositol and adenyl cyclase (RYBAKOWSKI 2003). Adenyl cyclase stimulates synthesis of cyclic adenosine monophosphate (cAMP), which in turn activates cellular albuminous kinase A, responsible for phosphorylation of many intracellular proteins (BULLOCK et al. 1997). In the process of inositol transformation, enzyme phospholipase C hydrolyzes phosphatidyloinositol diphosphate (PIP 2) into myoinositol triphosphate (IP 3) and di-acylglycerol (DAG). IP 3 stimulates releasing calcium ions from intracellular tanks; DAG in turn stimulates ac-

tivity of the cytosol enzyme, protein kinase C, which phosphorylates cellular proteins leading to its activation (BULLOCK et al. 1997). Re-synthesis of phosphatidylinositol requires participation of inositol monophosphatase in the breakdown of inositol monophosphate into alcohol. Blockage of this enzyme's action would make it impossible to synthesize IP 3 and DAG. Lithium decreases the activity of both inositol monophosphatase and protein kinase C, stabilizing cellular processes and expression of genes related to neurotransmitters (STAHL 2007). The normalizing influence of lithium on the phosphatidylinositol system has been demonstrated, for example, by was shown SILVERSTONE et al. (2002). Lithium probably activates the serotonin neurotransmitter system, inhibits the dopaminergic system and also changes the catecholamine metabolism (RYBAKOWSKI 2003). ANAND et al. (1999) proved that the mechanism of prevention of manic episodes was also stimulated by the stabilizing influence of lithium on the catecholamine system.

In these complex intracellular functions, lithium also leads to an increase in the cytokine concentration, activates cells of the immunity system, including granulocytes, and reveals the antiviral action. Neuroprotective and neurotrophic action of this element is probably linked to its influence on the growth factors being activated the central nervous system as well as the increase in the grey matter amount by activating neurogenesis processes (RYBAKOWSKI 2003, STAHL 2007). This fact seems to play a significant role, as suggested by the literature reports on functional and morphological abnormalities of brain cortex gyri in patients with affective diseases. SASSI et al. (2004) showed that in patients taking lithium there were no statistical differences in the volume of anterior brain gyrus volume compared to healthy controls. The authors relate this effect to the neuroprotective nature of lithium (SASSI et al. 2004). SILVERSTONE et al. (2003) and MOORE et al. (2000) report that in patients who continuously take lithium, there is an increase in the cortex N-acetyl-aspartate (NAA), which is a marker of neuronal viability and functionality

Despite introducing new agents to stabilize mood in therapy of affective disorders, lithium remains a medicine of the first choice (SHARMA et al. 1997, COMPTON, NEMEROFF 2000, SCULLY 2003). Some data show that lithium's efficacy in the treatment of depressive and manic episodes reaches 80% (SCULLY 2003). However, lithium salts have a delayed effect and in the early stages of acute maniac episodes treatment addition of other stabilizing agents is recommended (REISCHIES et al. 2002). Lithium is more effective in affective disorders following a classical course, i.e. with an average frequency of episode recurrences and moderate symptoms (KLEINDIENST, GREIL 2000, RYBAKOWSKI 2001). Lithium also seems to be more effective in the case of sequences of mania – depression (KLEINDIENST, GREIL 2000) and the coexistence of other psychiatric disorders worsens the response to this medication (KELLER et al. 2006). The Polish data show that in 30% of patients there is no recurrence of the disease and no burdensome side effects during the thera-

py with lithium (RYBAKOWSKI 2003). As far as the potentation of antidepressant action is concerned, clinical improvement is reached in half of all the cases (RYBAKOWSKI 1999). The anti-suicidal effect of lithium has been broadly documented in the literature. Meta-analysis by TONDO et al. (2001) showed that a long-term treatment with lithium salts decreases the risk of a suicidal attempt in all the analyzed cases.

SIDE EFFECTS AND COMPLICATIONS

Side effects of lithium involve its influence on the central nervous system, on the renal transport of electrolytes and the narrow therapeutic index of the medicine, which can be dangerous in the case of non-tolerance and may cause intoxication (SCULLY 2003, STAHL 2007). Severity of side effects increases together with an increase in the blood level of the medicine. GELENBERG et al. (1989) showed lithium salts were more effective in the concentration of 0.8-1.0 mmol dm^{-3} in the plasma than at the level of 0.4-0.6 mmol dm^{-3}. However, higher lithium concentrations caused the occurrence and intensification of side effects, including tremor of extremities, pollakiuria, diarrhoea, body weight increase and a metallic taste in mouth. A study conducted by ABOU-SALEH and COPPEN (1989) confirmed this relationship.

Another significant and common side effect of the administration of lithium is some distrubance of the water balance. It is manifested by polydipsia (excessive thirst) and polyuria (excessive urination) and occurs because lithium impaires the renal ability to concentrate urine through blockage of the antidiuretic hormone in renal tubules. The literature reports cases of nephrogenic diabetes insipidus during the therapy with lithium salts (PUŻYŃSKI, BERĘSEWICZ 1993, STAHL 2007). Usually, after a dose decrease, compensation of renal functions appears in a few months (SCHOU 2006). Cases of renal failure due to interstitial nephritis in the course of lithium therapy are very rare (STAHL 2007). Some early experiments on the lithium influence on the kidneys showed that in the first days of the treatment, cytoplasm vacuolization and glycogen cumulation in the cells of the renal distal nephrons and collecting tubules appeared (WALKER et al. 1983), although there is no evidence that lithium causes permanent renal lesion (RYBAKOWSKI 2003).

There are some initial and transient adverse event appearing during lithium therapy at the same frequency, like nausea, stomachaches, diarrhoea and loss of appetite and weakness (PUŻYŃSKI, BERĘSEWICZ 1993).

Some disturbances in the cardiovascular system are more seldom and appear at the beginning of lithium therapy (RYBAKOWSKI 2003). The literature reports cases of bradycardia, decrease in the arterial blood pressure, cardiac dysrhythmias and a sick-sinus syndrome (STAHL 2007). The non-specific ECG changes observed at the beginning of the therapy tend to regress during a long-term lithium therapy (RAJEWSKA, RYBAKOWSKI 1995).

There are some reports on an adverse effect of lithium adverse on the bone metabolism (Misra 2004). Tests completed by El Khoury et al. (2002) showed that a long-term lithium therapy leads to disturbances in the calcium metabolism manifested as mild hypercalcemia. Using lithium for more than 6 months also causes a decrease in prolactin (Basturk et al. 2001). The effect of lithium on aldosterone secretion may be a reason for oedema, which sometimes appears during lithium therapy (Pużyński, Beręsewicz 1993).

Lithium may cause a decrease in libido and erectile dysfunctions in men. However, such negative effects are rare and it has not been conclusively established if they are not due to possible symptoms of depression (Rybakowski 2003, Schou 2006).

Depression can also intensify cognitive disturbances that appear during lithium therapy. Despite the reports suggesting that lithium worsens thinking capabilities and the ability to remember or even inhibits creativity (Schou 2006), long-term observations concerning people taking this medicine prove that by maintaining remission of mood disorders, lithium leads to improvement of psychosocial (including occupational and interpersonal) functions in patients. The better lithium level in blood(according to standards), the better the effect (Solomon et al. 1996). Inferior cognitive functions can be attributed to the toxic lithium influence on the central nervous system, similarily to somnolence, headaches and vertigos (Rybakowski 2003). Serious neurotoxic symptoms of lithium are nystagmus, extrapyramidal symptoms, akathisia and, most often, ataxia and dysarthria. Such symptoms significantly worsen the patients' quality of life, require quick medical intervention and a cautious assessment in terms of possible lithium intoxication (Pużyński, Beręsewicz 1993, Kores, Lader 1997).

Lithium intoxication can be accidental (due to lack of control of the lithium blood level), suicidal or caused by the inferior renal elimination of lithium (in renal and circulatory dysfunctions, dehydration or excessive loss of sodium). It is the most serious complication of lithium therapy. According to the literature, is appears when the lithium level in plasma exceeds 1.6--1.8 mmol dm^{-3}. Symptoms of lithium intoxication are the aforementioned neurological symptoms and nausea, vomitting, diarrhoea, tremor, great weakness, consciousness disturbances, cardiac dysrhythmias, convulsions, circulatory and renal failure (Pużyński, Beręsewicz 1993, Rybakowski 2003, Pużyński 2009).

There are some conditions when lithium therapy requires great care or even discontinuation, which is due to the narrow therapeutic index of this element. These are the conditions when rapid accumulation of lithium in the body is possibile or when the toxic effect of lithium appears even though its level in plasma is within the normal values. Such conditions include dehydration, renal and circulatory disorders, lesions of the central nervous system with dementia, Parkinson's disease, epilepsy and hypothyroidism (Stahl 2007, Pużyński 2009).

Lithium can cause a non-toxic goitre or a goitre involving hypothyroidism. This effect is due to the inhibition of the secretion of thyroid hormones caused by lithium and can lead to the appearance of the symptoms of hypothyroidism (Schou 2006, Stahl 2007).

Among more common adverse symptoms during lithium therapy is weight gain. On average, patients put on about 4 kg, usually during the first year of the therapy and this effect more often concerns women (Schou 2006, Stahl 2007).

Lithium can cause exacerbation of the existing dermatological disorders, for example psoriasis, and can reduce the response of these disorders to pharmacotherapy. Lithium can also cause new dermal lesions such as acneform, psoriasisform lesions, sycosis, maculopapular eruption. Alopecia areata appears in 10% patients treated with lithium (Gupta et al. 1995, McKinney et al. 1996). Lithium administration can also lead to hyperglycemia and leucocytosis (Pużyński, Beręsewicz 1993, Pużyński 2009).

Most of the aforementioned side effects appear at the beginning of lithium therapy and disappear spontaneously or after adjusting the lithium level in plasma. Mauri et al. (1999) showed that there were no statistically significant differences in lithium tolerance in any period of its administration, from the first day to twenty-first year of therapy. Complications can be prevented by appropriate classification of patients for lithium therapy, which takes into consideration relative and unconditional contraindications. According to the literature, renal and circulatory dysfuntions, inadequate water-electrolyte balance, hypothyroidism, pregnancy and breast-feeding are unconditional contraindications for lithium therapy (Pużyński, Beręsewicz 1993).

Lithium ions pass through the placenta so that their level in the fetus's plasma is equal to the level in the mother's plasma (Pużyński, Beręsewicz 1993). Pinelli et al. (2002) reviewed the literature concerning the involvment of lithium in perinatal complications. Newborns of mothers treated with lithium most often suffer from congenital heart diseases, especially Ebstein's syndrome, cardiac dysrhythmias, decreases in the plasma glucose level, decreases of arterial blood pressure, respiratory failure, cyanosis, coma, disturbances of the thyroid function and hyperbilirubinemia. Most of the side effects of lithium's toxic influence on a fetus are transient and have no effect in the later childhood.

Adolescents are a specific target group for lithium therapy. Lithium is registered for therapy of persons above 12 years of age. Administration of lithium in the developmental period requires particular caution because of the altered pharmacokinetics of this medicine. High vulnerability of young organisms to disorders in the hormonal balance (Rajewski 2003), larger volumes of systemic water, higher speed of filtration in renal glomerules and high risk of lithium toxic effect on the developing central nervous system can limit administration of lithium in this age group (Tueth et al. 1998). On the other hand, elderly people have smaller volumes of systemic water, slow-

er metabolism and, often, coexisting somatic disorders complicating this therapy and exposing them to a higher risk of adverse events, thus lithium therapy in this group requires lower lithium concentrations in plasma (TUETH et al. 1998, STAHL 2007).

Simultaneous administration of medicines that interact with lithium requires great caution in lithium therapy. Medicines increasing the plasma level of lithium and thus increasing the risk of its toxicity are, for example, non-steroid anti-inflammatory agents, inhibitors of angiotensin converting enzyme and tiazids. Lithium should be used with caution also in the case of simultaneous therapy with metronidazol, methyldopa, phenytoin, haloperidol, carbamazepin and antidepressant agents with serotoninergic activity (RYBAKOWSKI 2003, STAHL 2007).

QUALITY OF LIFE OF PATIENTS TAKING LITHIUM

Good co-operation with patients during lithium therapy diminishes the risk adverse events and complications and thus can improve patients' quality of life. On the other hand, patients' negative attitude to lithium therapy, partial response or, on the contrary, great improvement which gives a feeling of absolute recovery, can cause termination of therapy. Discontinuation of lithium therapy can also be caused by some burdensome side effects or the patient's disapproval of the need of periodical laboratory and clinical tests, which are necessary for appropriate lithium therapy (SCHOU 2006). VIETA (2005) reports that psychoeducational interventions concerning identification of symptoms of disease recurrence, requirement of systematic maintenance treatment, conducting stabilised lifestyle improve the response to lithium therapy, decrease the number of disease recurrences and hospitalisations and improve patients' quality of life. DOGAN and SABANCIOGULLARI (2003) studied the influence of education about lithium therapy on the severity of symptoms and patients' quality of life. At the end of a three-month-long observational period, the group receiving psychoeducational instruction had better knowledge about the medicine, improved its taking, had fewer side effects and improved their quality of life. SCOTT and TACCHI (2002) proved that compliance with and acceptance of lithium therapy means maintaining optimal levels of the lithium concentration in plasma.

Many authors report that the presence of depressive symptoms prevails in the shaping of the quality of life in people with affective disorders. MONTES et al. (2008) assessed a group of 115 patients with bipolar affective disorder, in which 71.3% were treated with lithium salts. The authors showed correlation between worse subjective assessment of own quality of life and depressive symptoms. Lower quality of life in patients with affective disorder can be caused by the disorder itself, somatic reasons, using tobacco or

alcohol as well as side effects of the administered medicines. CHAND et al. (2004) showed that the quality of life in patients with bipolar affective disorder being stabilised with lithium was comparable with healthy controls. The authors relate this good result to fewer side effects during lithium therapy in comparison to the other mood stabilizators. Attaining an optimal response to treatment and preventing side effects as well as maintaining stabilizing therapy result in good quality of life. REVICKI et al. (2005) showed that patients treated with lithium for one year experienced improvement of mental health, which was was accompanied by lower medical costs (REVICKI et al. 2005).

CONCLUSIONS

Although lithium has been used in medicine for many years, during which new medications producing similar effects have been introduced, it remains a medicine of the first choice long-term stabilizing therapy, although, in the light of current research, lithium monotherapy in acute manic conditions or severe and moderate depressive episodes is not recommended (RYBAKOWSKI 2003). We can prevent complications related to lithium therapy and achieve satisfactory improvement as well as good quality of life, having considered in great detail possible contraindications for lithium therapy and later monitoring of its plasma level and observing the patient to detect any side effects.

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