http://dx.doi.org/10.5272/jimab.2014204.519

Journal of IMAB
ISSN: 1312-773X
http://www.journal-imab-bg.org

OPEN ACCESS

Journal of IMAB - *Annual Proceeding (Scientific Papers)* 2014, vol. 20, issue 4

LITHIUM TOXICITY IN ELDERLY-A CASE REPORT AND DISCUSSION

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SUMMARY

Background: The therapeutic effect of Lithium as a mono therapy or as an augmenting agent in a variety of medical and psychiatric disorders is under doubt. However, lithium is associated with a number of adverse effects.

Method and objective: A review of the literature on lithium use in older adults and a case report presentation.

Summary of results: The literature, concerning current uses of Lithium in older patients, especially for patients with neurologic or cognitive impairments is limited due to the lack of well-designed, large clinical trials. Elderly patients are at higher risk to develop neurotoxicity in the course of lithium therapy.

We present a case of 66 years old female patient, suffering bipolar disorder, who developed lithium toxicity and was admitted at the gerontopsychiatric department due to a confusional state, tremor and gait abnormality. Lithium toxicity was suspected when sufficient information about previous medical history of lithium therapy has been obtained. Lithium level found to be 1.69mmol/L. The patient has developed intoxication during maintenance therapy with a lithium dosage which had been unchanged for months.

Conclusion: Elderly patients require lower doses of Lithium to achieve similar serum concentrations as those in younger adults. Neurotoxicity could be suspected at serum lithium levels which are considered therapeutic in younger adults. When prescribing lithium agents in elderly we should consider age-related changes in pharmacokinetics. The best way to prevent lithium toxicity is to control the serum concentration regularly during therapy.

Key words: elderly; lithium toxicity; neurotoxicity; cognition

INTRODUCTION:

Lithium has a long medical history, which could be traced more than thousand years ago. Its introduction in modern medicine started with administration in a range of somatic problems. Observational studies in Japan, reported in 2011, suggested that naturally occurring lithium in drinking water may increase human lifespan [1].

The use of Lithium in psychiatry goes back to the mid-19th century but its introduction as a pharmacologic agent is in 50-ties last century. A number of its salts are used as mood-stabilizing drugs, primarily in the treatment of bipolar disorder. As a mood stabilizer, Lithium is probably more effective in preventing mania than depression, and reduces the risk of suicide in people with bipolar disorder [2]. In unipolar depression lithium can be used to augment other antidepressants or antipsychotics. A number of adverse events, especially in elderly, can lead to noncompliance [3]. Increased use of polypharmacy and co-morbid medical/psychiatric conditions in older adults results in potential drug interactions.

This article examines the clinical presentation of adverse events, predominantly neurological, associated with lithium intoxication in a patient on maintenance therapy with a lithium carbonate.

METHOD AND OBJECTIVE:

A review of the literature on lithium use in older adults and a case report presentation.

RESULTS AND DISCUSSION:

The literature, concerning current uses of Lithium in older patients, especially patients with neurologic or cognitive impairments, is limited due to the lack of well-designed, large clinical trials. The suggestions for use in clinical practice are based mostly on data from pharmacokinetic studies and clinical experience in old age psychiatry [4, 5].

The exact mechanisms of lithium action in the treatment of bipolar patients remain unclear yet. Two enzymatic chains or pathways emerge as targets for Lithium: inositol monophosphatase within the phosphatidylinositol signalling pathway and the protein kinase glycogen synthase kinase 3. Lithium inhibits these enzymes through displacing the normal cofactor magnesium, a vital regulator of numerous signalling pathways. Inhibition of these enzymes by lithium can lead to downstream effects of clinical relevance, both for mood disorders and neurodegenerative diseases [6].

Elderly patients usually have physical and psychiatric comorbidities, chronic course of illnesses, incomplete therapeutic response. They are more sensitive to side effects and toxicity of psychotropic drugs, the consequences, being severe and disabling [7, 8, 9]. Generally, aging is characterized by progressive impairment of functional capacities of all system organs, reduction in homeostatic mechanisms, and altered response to receptor stimulation. Significant differences in the response to several drugs in same drug concentrations have been

observed in older patients as compared to younger ones [10].

Renal function also declines with aging, mainly due to sclerotic changes in the glomeruli. A clinically not manifested renal insufficiency may impact significantly the clearance of hydrosoluble drugs. Older subjects with reduced muscle mass frequently have depressed glomerular filtration rate despite normal serum creatinine [11].

Age-related physiologic changes influence both pharmacokinetics and pharmacodynamics of drugs in elderly patients and together with co-morbidity and polypharmacy set elderly patients of risk for complications Due to pharmacodynamic changes dose adjustment of cardiovascular and psychotropic drugs is recommended in elderly [4, 10]. Thiazide diuretics, Angiotensin-converting enzyme (ACE) inhibitors, and non steroidal anti-inflammatory drugs (NSAIDs) alter the serum lithium concentrations. Frequently prescribed drugs, acting on central nervous system, such as benzodiazepines, antidepressants, antipsychotics and Lithium could provoke serious adverse drug reactions. [11, 10, 4].

Serum concentrations of Lithium in older patients are associated with reduced volume of distribution and reduced renal clearance in patients with hypertension, congestive heart failure or renal dysfunction. Some case reports in older subjects indicate that lithium toxicity can occur at moderate blood levels (eg, 0.5–0.8 mEq/L) [4, 7].

In aged patients, brain/peripheral lithium concentration ratio can be increased and this may also increase vulnerability to central nervous system toxicity. Forester et al. (2008) found in a study of bipolar patients that serum lithium levels did not correlate with brain lithium levels in older patients. In addition, higher brain lithium levels, but not higher serum lithium levels, predicted greater executive dysfunction and somatic symptoms of depression in older subjects. They put an accent that some subtle signs of attention problems (that look like mild delirium or confusion), could be directing for toxicity even when older patients are on lower doses and lower target serum level of lithium [12, 13, 14].

We present a case of 66 years old female patient, suffering bipolar disorder, who developed lithium toxicity and was admitted at the gerontopsychiatric department due to a confusional state, tremor and gait abnormality.

At the admission the patient appeared confused, complaining of nausea, weakness, unstable gait, memory difficulties and severe anxiety.

On physical examination - asthenic habitus, reduced body mass, afebrile, pale dry skin. Lungs were clear to auscultation. Cardiovascular examination revealed rhythmic heart action; Blood pressure was 125/85 mm/Hg, P70; Electrocardiography was normal; abdomen was insensitive.

Neurological exam revealed coarse tremor of body and hands, gait ataxia. Hand tremor increased under pressure.

Mental status at the time of assessment- the patient was anxious, agitated, fidgeting and pacing during the interview. Though oriented to place and person, she looked confused with difficulty focusing and sustaining attention and short-term memory difficulties. The patient reported of mild sleep continuity disturbance at night and drowsiness during the day.

Lithium toxicity was suspected when sufficient information about previous medical history of lithium therapy has been obtained. Lithium level found to be 1.69 mmol/L. The patient had been on maintenance therapy with a lithium carbonate dosage 450 mg twice daily, which had been unchanged for months. Plasma levels of Lithium were not examined regularly. Drug history included Lisinopril 10mg/day, Torvalipin (Atorvastatin) 10 mg/day, Moxotens (Moxonidine) 0.2 mg/day, Furanthril (Furosemide) 40 mg/day.

Laboratory values of hematology and biochemistry, including creatinine, were in normal ranges. CT scan of the head ruled out other etiologies.

Although the plasma value of Lithium was comparatively mildly elevated, neurotoxicity was produced, leading to severe neurological symptoms.

The basic principle of lithium intoxication management is enhanced elimination. Fluid therapy is the mainstay of treatment. Most patients with lithium intoxication are volume depleted and require intravenous rehydration. The goal of saline administration is to restore glomerular filtration rate (GFR), normalize urine output, and enhance lithium clearance.

The patient was commenced on IV fluid hydration with isotonic Sodium chloride solution 1000 ml/daily and Mannitol 250 ml in-between for 7 days. Lisinopril and Furanthril were discontinued. Lithium levels decreased to 0.39 mmol/L. After 20 days the patient was discharged in a stable general and psychic state and adapted to Valproic acid (Convulex) 600mg/daily.

What important lessons we could learn, recall and remember?

Our case highlights few important points. Lithium has a relatively narrow therapeutic index that predisposes patients, especially older ones, on chronic maintenance treatment to lithium intoxication and neurotoxicity at serum levels which are considered "therapeutic" in younger adults. There is also a difference in lithium tolerability with age, and the prevalence of hand tremor with lithium increases with age [5, 15]. The dosage and serum concentrations of lithium need to be much reduced in the elderly population. Older patients require a dose 31% lower than those aged <50 years [16]. Guidelines for serum lithium concentrations are based on limited evidence; and a low mean serum lithium concentration (approximately 0.5 mmol/L), are recommended, which may be achieved using a mean dose of just over 400 mg/day in a single-dose regimen [17]. The dosage recommended by some authors amongst patients aged between 65 and 75 years ranges from 300 to 600 mg/day and rarely exceeds 900 mg/day. For patients aged more than 80 years or frail elderly, the dosage should range from 150 to 300 mg/day and should rarely exceed 450 mg/day [18].

Chronic lithium toxicity is usually precipitated with introduction of a medication that may impair renal function/

excretion or cause a hypovolemic state (Tabl. 1). Symptoms are primarily neurologic- altered consciousness, slurred speech, seizures, coma (Tabl. 2).

Tabl. 1. Important factors that increase the risk for lithium toxicity

Drug interactions
· Diuretics that promote renal sodium wasting
· Angiotensin-converting enzyme (ACE) inhibitors that reduce glomerular filtration rate (GFR) and enhance the tubular reabsorption of lithium
· Nonsteroidal anti-inflammatory drugs (NSAIDs) that reduce GFR and interrupt renal prostaglandin synthesis
Concurrent illness that decrease circulating volume
Alterations in serum potassium or sodium concentrations

Tabl. 2. Neurological symptoms, associated with lithium intoxication

	Acute intoxication	**Chronic intoxication**
Mild	Fine tremor, lightheadedness, weakness	**Same**
Moderate	Apathy, drowsiness, hyperreflexia, muscle twitching, slurred speech, tinnitus	**Same**
Severe	Choreoathetoid movements, clonus, coma, confusion, muscular irritability, seizures	Memory deficits, Parkinson's disease, Psychosis

If a patient shows signs of toxicity, lithium should be stopped immediately and the serum lithium levels, creatinine and urinalysis should be investigated.

Lithium is readily dialyzed because of water solubility, low volume of distribution, and lack of protein binding.

Hemodialysis is indicated for patients who have renal failure and are unable to eliminate lithium. It is also recommended in patients who develop severe signs of neurotoxicity. An absolute level of 4 mEq/L in acute toxicity and a level of 2.5 mEq/L in chronic toxicity in patients with symptoms should also be considered for hemodialysis (GF), although guidelines for hemodialysis based on levels alone are controversial. Because postdialysis rebound elevations in lithium levels have been documented, continuous venovenous hemofiltration (CVVH) has been advocated [18, 19].

CONCLUSIONS:

Mood stabilizer treatment has numerous acute and long-term adverse events. Narrow therapeutic index remains a major limitation of lithium treatment as it requires close monitoring and identification of neurologic adverse events. Selection of newer mood stabilizers should be based both on efficacy and safety according to risk and benefit. Patient education and psychological support about adverse events remains an important issue of lithium treatment management, thus improving patient compliance [20]. Patient compliance [21, 22] remains a major issue for patients being treated with mood stabilizers.

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Please cite this article as: Arnaoudova MD. Lithium toxicity in elderly-a case report and discussion. *J of IMAB*. 2014 Jul-Sep;20(4):519-522. doi: http://dx.doi.org/10.5272/jimab.2014204.519

Received: 30/04/2014; Published online: 25/07/2014

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