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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2016,4(2),66–68

Mini-Review

Hypercalcemia and hyperparathyroidism in long-term lithium administration

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Abstract

Lithium compounds are commonly used in the treatment and prophylaxis of mood disorders, multiple sclerosis, stroke insults, neurotoxicity associated to human immunodeficiency virus and Huntington disease. Although the clinical benefit of lithium salt has known over the long term, it is related to the risk of development of numerous adverse effects such as hyperparathyroidism and hypercalcemia. The exact pathogenic mechanism for abnormality or impairment in parathyroid during lithium therapy is however unknown. Lithium-associated hyperparathyroidism is often asymptomatic. The manifestations are resulted of the detrimental effects of chronic excessive secretion of parathyroid hormone following hypercalcemia to human body tissues. The calcium, parathyroid hormone and 1,25-hydroxycholecalciferol concentrations in blood should be monitored periodically during lithium treatment. Sometimes the cessation of lithium administration does not lead to normocalcemia, thus parathyroidectomy may indicate. Psychiatrists should be noted in screening for hyperparathyroidism and hypercalcemia in their older patients taking lithium, both prior to starting administration and at least annually thereafter.

Keywords: Lithium therapy, Parathormone, Intoxication, Calcium, Parathyroid hormone, Neurotoxicity

Please cite this paper as: Hedaiaty M, Hedaiaty M. Hypercalcemia and hyperparathyroidism in long-term lithium administration. J Parathyr Dis. 2016;4(2):66-68.

Introduction

Lithium compounds are commonly used in the treatment and prophylaxis of mood disorders, multiple sclerosis, stroke, neurotoxicity associated to human immunodeficiency virus and Huntington disease (1,2).

The use of it is limited by their narrow therapeutic index and practitioners have to routine monitor of serum concentrations of lithium (1). Although the clinical benefit of lithium salt has known over the long term, it is related to the risk of development of numerous adverse effects such as thyroid dysfunction, hyperparathyroidism, weight gain, acute parkinsonism and nephrogenic diabetes insipidus (3,4).

The prevalence of lithium-associated hyperparathyroidism was quite frequent (an absolute risk of 10% versus 0.1% of the general population) particularly in women and in individuals over 60 years or more and often remains hidden and most patients are asymptomatic and the diagnosis is only biochemical (4,5). However, the true and exact prevalence remains undetermined because of the lack of population based data.

Albert et al show that lithium could stimulate of parathyroid function and increase parathyroid hormone levels and ionized calcium levels in lithium-exposed patients with a rate of hyperparathyroidism of 8.6% event after 3 months of continued exposure to lithium (6,7).

Hyperparathyroidism is affiliated to increased risk for cardiovascular disease, hypertension, renal stones, renal failure, bone fractures, cancer and diabetes (8).

Chronic lithium therapy has been associated with metabolic disturbances such as hypercalcemia and hypovolemic hypernatremia (4).

Materials and Methods

While, lithium is one of the most widely drugs in psychiatry and according to its side effects, we aimed to conduct an updated mini-review on chronic administration of lithium.

For this mini-review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; lithium therapy, parathyroid glands, calcium, parathyroid hormone and parathormone. Titles and abstracts of articles were investigated of review articles, clinical trials, cohort studies, case-control studies, and reports that were relevance to the intended topic. Lithium-associated hyperparathyroidism is a disorder that affects multi-organ systems.

Pathophysiology

Lithium may alter calcium homeostasis by several mech-

Received: 29 February 2016, Accepted: 25 May 2016, ePublished: 5 June 2016

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Implication for health policy/practice/research/ medical education

Lithium-associated hyperparathyroidism is often asymptomatic. The manifestations are resulted of the detrimental effects of chronic excessive secretion of parathyroid hormone following hypercalcemia to human body tissues. The calcium, parathyroid hormone and 1,25-hydroxycholecalciferol concentrations in blood should be monitored periodically during lithium treatment. Sometimes the cessation of lithium administration does not lead to normocalcemia, thus parathyroidectomy may indicate. Psychiatrists should be noted in screening for hyperparathyroidism and hypercalcemia in their older patients taking lithium, both prior to starting administration and at least annually thereafter.

anisms. Lithium acts directly on bowel and renal tubules stimulating calcium reabsorption, independently of parathyroid hormone. Moreover lithium has direct stimulatory effects on the "set point" at parathyroid glands that strengthen parathyroid hormone release in response to rising serum calcium levels (9).

Previous studies have not defined the main etiology of lithium-associated hyperparathyroidism (4,6,7). It is not clear whether lithium by itself initiates these diseases. However an underlying state of hyperparathyroidism may be possible. The exact pathogenic mechanism for abnormality or impairment in parathyroid during lithium-treated is still unclear. It may be associated with a direct influence of lithium on both the growth of parathyroid tissue and decrease parathyroid cell sensitivity to calcium. Total calcium and ionized calcium levels may not increase during lithium therapy in all cases. Several hypothesis on the underlying mechanism of lithium-hyperparathyroidism have been proposed including increased threshold of the calcium sensing receptor in the parathyroid gland and interference with intracellular second messenger signaling that leads to a release raise of parathyroid hormone, reduction of the intracellular calcium uptake, increased calcium concentrations in blood, inhibition of function of glycogen synthase kinase-3ß and decrease of parathyroid hormone gene transcription (4,6,7). In addition, lithium may induct of parathyroid hyperplasia, adenomas and increase the incidence of multiglandular disease (10). There was controversial report that there was not increase the frequency of multiglandular disease in lithium-associated hyperparathyroidism patients versus patients with primary hyperparathyroidism without lithium administration. (11).

Calcium level maintenance between a narrow physiologic rang is reachable by an inverse sigmoidal relationship between parathyroid hormone levels and serum ionized calcium. This relationship is mediated through G-protein-coupled calcium-sensing receptors, which are highly expressed in the parathyroid gland and kidneys (12). Lithium intoxication may cause through nephrogenic diabetes insipidus and dehydration related to the hypercalcemia (13). In addition, long term lithium administration can cause renal resistance to parathyroid hormone, renal tubular acidosis, aminoaciduria, proteinuria and reduced glomerular filtration rate that lead to electrolyte disturbance (13).

However, it is not well-known whether lithium dose and the duration of exposure to lithium are exactly related to parathyroid hormone or calcium levels (6,7).

On the other hand, hypercalcemia and hyperparathyroidism have the same etiologically related to nephropathy of lithium therapy (14). A little increased in serum calcium-ion concentration in concert with plasma volume depletion resulting to diabetes insipidus and/ or reduced calcium excretion. This condition in patients with renal failure may cause nephrolithiasis or nephrocalcinosis too (15).

Clinical manifestations

Lithium-associated hyperparathyroidism could present either as symptomatic form or as asymptomatic form. Also it is rarely formed as an acute hypercalcemic crisis. However, it may be represented with normocalcemia on the first stage of the disease. In symptomatic forms, manifestations are resulted of the injurious effects of chronic excessive secretion of parathyroid hormone following hypercalcemia to human body tissues. They are parallel to the extent of serum levels of parathyroid hormone and calcium (8). Vitamin D insufficiency is common and has the potential to affect clinical presentation toward deterioration. However, hyperparathyroidism often remains undetected and having no objective manifestations of the disease. They may have vague neurocognitive symptoms or altered quality of life such as pain, fatigue, depression and constipation (5-8).

Lithium-associated hyperparathyroidism is a disorder that affects multi-organ systems. It may occur more frequently in older patients. Its symptoms include lethargy, drowsiness, weakness, nausea, vomiting, diarrhea, impaired consciousness, ataxia, seizures, cardiac arrhythmias, renal insufficiency and acute renal failure (4,8,16).

Managements

In spite of the fact that, several psychiatric consensus guidelines reference to the management of lithium intoxication, only one guideline recommends routine calcium and parathyroid hormone screening in lithium-treated patients (9). In chronic lithium users, the bone mineral decreased, in association with elevation of serum levels of immunoreactive parathyroid hormone, calcium and magnesium during the treatment with lithium. Psychiatrists should note in screening for hyperparathyroidism and hypercalcemia in their older patients taking lithium, both prior to starting administration and at least annually thereafter (3). If clinical symptoms are reported, specific follow-up including the monitoring of calcium, parathyroid hormone and 1, 25-hydroxycholecalciferol concentrations every year or more frequently is recommended. Moreover during the treatment, the bone mineral may de-

crease and the serum levels of magnesium may increase, thus, it is better to monitor the bone mineral and the serum levels of magnesium too. Psychiatrists should be considered with intention to improve psychiatric well-being and provide multi-organ protection. The balance of risks should be considered before lithium withdrawn (5).

In this regards, a study suggests that patients with pre-existing parathyroid disorders may be susceptible to the development of lithium associated hyperparathyroidism. Often cessation of lithium treatment normalizes parathyroid function, but the hypercalcemia may not occasionally resolve the problem. Thus, parathyroidectomy may be necessary only in some cases. Concordant sestamibi scintigraphy and ultrasound imaging are the sensitivity and specificity for identifying single-gland versus multiglandular involvement (17). Lithium-induced hyperparathyroidism presents with a spectrum of disorder ranging from single-gland to four gland disease characterized by asymmetrical hyperplasia. Bilateral exploration may be best way to achieve a resolution of it. If localization offers single gland disease, minimally-invasive parathyroidectomy plus intraoperative parathyroid hormone monitoring may be successfully performed. Surgery provided a safe and effective management option with a long-term cure rate of well over 80% (17).

Conclusion

Lithium-associated hyperparathyroidism is often asymptomatic. The manifestations are resulted of the detrimental effects of chronic excessive secretion of parathyroid hormone following hypercalcemia to human body tissues. The calcium, parathyroid hormone and 1,25-hydroxycholecalciferol concentrations in blood should be monitored periodically during lithium treatment. Sometimes the cessation of lithium administration does not lead to normocalcemia, thus parathyroidectomy may indicate. Psychiatrists should note in screening for hyperparathyroidism and hypercalcemia in their older patients taking lithium, both prior to starting administration and at least annually thereafter.

Authors' contribution

MH and MH wrote the manuscript equally.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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