Lithium therapy and thyroid disorders

Lit a zaburzenia tarczyczne

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Summary
Lithium is approved for the treatment of acute mania and bipolar disorder and also as long-term prophylaxis of bipolar disorders. Lithium highly concentrates in the thyroid gland against a concentration gradient, probably by active transport. It acts in multiple directions, in particular, inhibiting the thyroid hormone release from thyroid gland, increasing the iodine content in the thyroid gland, inhibiting the coupling the iodotyrosine residues to form iodothyronines tyroxine and triiodothyronine. Lithium may cause goiter and hypothyroidism, as well as autoimmune thyroid disease. Goiter is noted in about 40-50% of patients. The incidence of hypothyroidism is less frequent in lithium-treated patients but is still 2-3 time higher than in the general population. Prior to lithium administration, patients should undergo a physical examination of the thyroid gland and estimation of TSH and antithyroid peroxidase antibodies and/or ultrasound of the thyroid gland. Re-evaluation is recommended every 6 to 12 months. Thyroid dysfunction usually requires treatment without the need to discontinue lithium. Because of its ability to inhibit thyroid hormone secretion, lithium can be used to treat thyroid diseases including hyperthyroidism. It is not used as a first-line treatment because of the side effects and the availability of other potent antithyroid agents. The ability to increase thyroid iodine retention may be used to augment the efficacy of radioactive treatment.

Streszczenie
Lit jest rekomendowany do leczenia ostrej manii i choroby afektywnej dwubiegunowej, a także jako długotrwała profilaktyka zaburzeń dwubiegunowych. Lit gromadzi się w gruczołach tarczowym wbrew gradientowi stężeń i działa wielokierunkowo, powodując hamowanie proteolizy, czyli uwalniania hormonów z gruczołu tarczowego, zwiększenie zawartości jodu w gruczołach, hamowanie sprzęgania reszt tyrozynowych do tyroksyny i trijodotyroniny. Może powodować wole i niedoczynność tarczycy, a także autoimmunizacyjną chorobę tarczycy. Wole stwierdza się u około 40-50% leczonych, niedoczynność tarczycy u 20-30%, nadczynność tarczycy 2-3-krotnie częściej niż w ogólnej populacji. Przed podaniem litu chorzy powinni odbyć badanie fizykalne tarczycy i oznaczenie stężenia TSH oraz przeciwciał przeciw peroksydazie tarczycznej i ultrasonografię tarczycy. W czasie leczenia zalecana jest ponowna ocena co 6-12 miesięcy. Zaburzenia czynności tarczycy wymagają leczenia zwykle bez konieczności odstawiania litu. Z uwagi na zdolność do hamowania wydzielania hormonów tarczycy lit może być zastosowany w leczeniu chorób tarczycy, w tym nadczynności. Nie jest stosowany jako leczenie pierwszego wyboru ze względu na działania niepożądane i dostępność innych silnie działających leków przeciw- tarczycowych. Zdolność do zwiększenia retencji jodu w tarczycy może być wykorzystana celem zwiększenia skuteczności leczenia radioiodem.

INTRODUCTION
Lithium, an element in the alkali metal group, is approved for the treatment of acute mania and bipolar disorder and also as a long-term prophylaxis of bipolar disorders (1). Lithium act by substituting potassium ions, which affects the ratio of these ions inside and outside the cell. These changes may affect the release of certain neurotransmitters and their uptake. Lithium plays a neuroprotective role, increasing gray matter volume in several brain areas including the amygdala, hippocampus and prefrontal cortex. At the cellular level lithium decreases excitatory and increases inhibitory...
neurotransmission. Lithium is available only for oral administration as lithium carbonate salt. It is almost completely absorbed from the gastrointestinal tract. Peak levels occur in 2-4 hours. The plasma elimination half-life of a single dose of lithium takes from 12 to 27 hours. Lithium is almost exclusively excreted by the kidneys and dosing must be adjusted to the renal function. Most filtered lithium is reabsorbed in the proximal tubule. Reabsorption of lithium is increased in patients who are hyponatremic or volume depleted, both of which are possible consequences of diuretic therapy. The therapeutic dose to obtain the desired therapeutic serum levels of 0.6-1.2 mEq/L is 300-2700 mg/d (2).

LITHIUM SIDE EFFECTS AND TOXICITY

While it is effective drug for the treatment of bipolar disorders, lithium therapy is associated with risk of toxicity even when blood level is in narrow therapeutic window (2). Elderly patients may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients. The central nervous system is the major system affected, although the renal, gastrointestinal, endocrine, and cardiovascular systems also may be involved (3). Lithium toxicity may be of an acute or chronic nature. Acute intoxication manifestations are predominantly gastrointestinal, but progression to neuromuscular signs may occur, acute-on-chronic both gastrointestinal and neurologic manifestations may be also present, whatever chronic manifestations are primarily neurologic. Acute toxicity occurs typically in the setting of accidental or intentional overdose. Diarrhea, vomiting, somnolence, muscular weakness and lack of coordination may be early signs of lithium toxicity, and can occur at lithium concentrations below 2.0 mEq/L. At higher concentrations, dizziness, ataxia, blurred vision, tinnitus and a large output of dilute urine may be seen. Serum lithium concentrations above 3.0 mEq/L may cause a complex clinical picture involving multiple organs and organ systems with coma, and eventually death. Chronic toxicity often manifests as gradual development of neurological symptoms similar to those of late phase of acute toxicity. Chronic lithium treatment may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Lithium can cause hyponatremia by decreasing sodium reabsorption by the renal tubules, leading to sodium depletion. It can also cause chronic tubulointerstitial nephropathy. An encephalopathic syndrome, characterized by weakness, lethargy, fever, tremulousness and confusion and extrapyramidal symptoms has occurred in patients treated with lithium and an antipsychotic. Lithium can precipitate serotonin syndrome, a potentially life-threatening condition. Long-term lithium treatment is associated with persistent hyperparathyroidism and hypercalcemia. There have been reports of a possible association between treatment with lithium and the unmasking of Brugada syndrome. Brugada syndrome is a disorder characterized by abnormal electrocardiographic findings and a risk of sudden death. Pseudotumor cerebri characterized by increased intracranial pressure and papilledema have been reported with lithium use. The risk of lithium toxicity is especially high in patients with significant renal or cardiovascular disease, severe dehydration or sodium depletion, and in patients receiving medications that may affect kidney function, such as angiotensin converting enzyme inhibitors, diuretics loops and thiazides and nonsteroidal anti-inflammatory drugs (indomethacin, piroxicam, selective cyclooxygenase-2 (COX-2) inhibitors). Accurate lithium treated patient’s evaluation requires both clinical and laboratory analysis. Before initiating treatment with lithium, renal function, serum electrolytes and thyroid function should be evaluated. There have been no adequate studies conducted to evaluate the mutagenic potential of lithium. Due to potential risk to the fetus and neonate, lithium can not be recommended during pregnancy and breast-feeding (1). Lithium is contraindicated in patients with known hypersensitivity to any ingredient in the lithium carbonate tablet. No specific antidote for lithium poisoning is known. Early symptoms of toxicity can usually be treated by reduction or cessation of lithium. Treatment of lithium intoxication depends on the degree of toxicity. In cases of mild toxicity lithium discontinuation may be sufficient. Moderate toxic episodes require fluid infusion with saline diuresis. The most severe cases defined by extraordinarily high lithium levels above 4 mmol/l or marked clinical symptoms may require hemodialysis (4).

LITHIUM AND THYROID

Lithium highly concentrates in the thyroid gland against a concentration gradient, probably by active transport. In clinically useful doses, lithium, like iodine decreases the release of preformed thyroid hormones from the thyroid. Its primary effect seems to be the blockade of colloid droplet formation in the apical pole of the thyrocyte and hence, inhibition of thyroid hormone release, a process stimulated by thyrotropin and mediated by cyclic adenosine monophosphate (cAMP) within the thyrocyte. Lithium alters the structure of thyroglobulin, thereby affecting protein conformation and function and resulting in a clinical picture of a mild iodotyrosine coupling defect. Finally, lithium reduces hepatic deiodination and clearance of free thyroxine (T4) (5, 6). The latter induces a decrease in the activity of type I 5’-deiodinase enzyme. The inhibition of thyroid hormone secretion results in decreased serum T4 and T3 concentrations, a compensatory increase in pituitary secretion of thyrotropin (TSH) and secretion of a normal amount of thyroid hormone by an enlarged thyroid gland. Thyroid enlargement may also occur as a result of lithium induced alterations in the function of insulin-like growth factor, tyrosine kinase, and/or Wnt/beta-catenin signaling (7). The tendency of the thyroid gland to “escape” the inhibitory effects of lithium is similar to that observed with iodine, although it is less marked. Because of a risk of the thyroid dysfunction in
lithium treated patients thyroid parameters should be checked before lithium is instituted and then monitored after 6-12 months. All patients should undergo physical examination and a laboratory evaluation, including serum TSH and antithyroid antibodies (TPO), ultrasound of the thyroid gland is also recommended. If thyroid function is abnormal at the initial evaluation, lithium can still be given if necessary but the thyroid dysfunction should be treated.

**GOITER**

Goiter, the thyroid enlargement, is the most common thyroid abnormality in lithium treated patients (8). The prevalence of goiter in patients receiving lithium therapy is higher in patients from iodine-deficient areas. It occurs in 40-50% of European patients. In the USA the prevalence of goiter in patients receiving the lithium therapy is approximately 15-20%. In affected patients the goiters usually occur within the first two years of treatment, enlargement proceed to about twice the normal size, and the goiter is usually diffuse although nodular goiter has also been reported. Older patients are more prone to the development of this abnormality. No differences in the incidence or prevalence of goiter have been reported between men and women. The diagnosis and treatment of goiter in patients taking lithium is the same as for goiter of any etiology. Ultrasound evaluation is typically performed to assess diffuse versus nodular enlargement. Further evaluation of nodular thyroid disease with fine needle aspiration biopsy may be indicated. Levothyroxine treatment may stabilize or reduce thyroid enlargement in patients with lithium-induced goiter. Lithium treatment should not be discontinued. It is unusual for lithium to cause large obstructive goiter but in such cases surgery or radiiodine therapy are an alternative treatment (9, 10).

**HYPOTHYROIDISM**

About 20% of patients receiving lithium therapy who develop goiter i.e. 8-23% of all patients on lithium therapy, has concomitant hypothyroidism (11). As mention above no differences in the incidence or prevalence of goiter have been reported between men and women, although lithium-induced hypothyroidism is more common in women. Hypothyroidism occurs mostly in individuals predisposed to the thyroid failure, with positive antithyroidal antibodies or with a prior history of thyroid gland damage following external radiation or iodine-131 therapy administered to treat previously diagnosed hyperthyroidism. The overall risk of hypothyroidism in patients treated with lithium occurs during the first two years of lithium treatment. It increases with age, specially women over 45 years old are at greater risk of lithium-induced hypothyroidism. Hypothyroidism can be subclinical with an elevated thyroid stimulating hormone (TSH) level, and normal T4 and T3 levels with few signs or symptoms. In some cases, the hypothyroidism is mild and transient, and thyroid function returns to normal. A small percentage of patients, however, will develop overt hypothyroidism with its typical signs and symptoms. These patients should be treated with levothyroxine according to the general therapeutic guidelines. Lithium treatment need not be discontinued and as a rule should not be discontinued without consultation with the patient’s psychiatrist. Neither lithium-induced goiter nor hypothyroidism causes mortality directly. Local compressive symptoms from concomitant thyroid enlargement like dysphonia, dysphagia, voice-quality changes and neck discomfort may occur (8).

**CHRONIC AUTOIMMUNE THYROIDITIS**

It is likely that many patients who develop hypothyroidism during lithium treatment have underlying chronic autoimmune thyroiditis. They have a greater prevalence of antithyroid antibodies before lithium is begun than those lithium-treated patients who remain euthyroid. However, whether lithium itself can induce thyroid autoimmunity is unknown. In one study, the incidence of antithyroid antibodies was higher in depressed patients who were treated with lithium than in depressed patients who were treated with other drugs. Other studies show fluctuations in antithyroid antibodies in patients pre- and post-lithium therapy (12, 13).

**LITHIUM INDUCED AUTOIMMUNITY**

Some authors demonstrated that lithium could induce autoimmunity. They found that 20% of lithium-treated patients presented anti-thyroid antibodies compared to only 7.5% in patients not receiving lithium therapy. In addition, they reported that lithium caused an increase in B-cell activity and a decrease in the ratio of suppressor T cells to cytotoxic T cells, a possible mechanism for lithium’s immunogenic properties. On the other hand, thyroid autoimmunity per se is highly prevalent in patients with bipolar disorder (12, 13).

**HYPERTHYROIDISM AND THYROTOXICOSIS**

Hyperthyroidism is a condition that occurs due to excessive production of thyroid hormones by the thyroid gland. The frequency of hyperthyroidism in patients treated with lithium is two to three times greater than in the general population. Thyrotoxicosis resulting from inflammation of the thyroid gland, which causes the release of stored thyroid hormone can also be observed in lithium-treated patients, but it is rare with a prevalence of 0.7%. The treatment of hyperthyroidism in lithium-treated patients depends upon the cause. This usually includes symptomatic treatment with beta-blockers and antithyroid medications with thionamides, radiiodine-131. Surgery is indicated for patients with large, obstructive goiters, who are allergic to antithyroid medication and for those who don’t accept the radiiodine therapy. In patients with lithium-induced thyroiditis conservative management with close follow-up is recommended (14, 15, 25).
LITHIUM TREATMENT OF THYROID DISORDERS

Lithium induced inhibition of thyroid hormone secretion could be adjunct therapy for some patients with hyperthyroidism or thyroid cancer (16, 17). However, it is not used as first-line therapy because of side effects and the availability of other antithyroid drugs thionamides. Lithium in a dose of 600 to 1000 mg/day, is effective therapy for patients with hyperthyroidism. Its effects on thyroid hormone secretion are quantitatively similar to those of iodide, and therefore may be given in place of iodide in patients who would it benefit from rapid correction of hyperthyroidism but are allergic to iodine. It also may be useful in patients with intolerance to thionamides. Lithium may prolong the retention of radioiodine within the thyroid gland, which could increase the effectiveness of radioiodine therapy. In a retrospective cohort study, the cure rate was slightly higher in patients given lithium in a dose of 900 mg/day for 12 days starting five days before radioiodine (91 vs 85%; P = 0.03), but there was no difference in randomized trial of radioiodine alone versus radioiodine plus lithium 900 mg/day. Lithium given coincidently with radioiodine can prevent the transient increase in serum thyroid hormone concentrations following radioiodine (18-20). Because of inconsistent data and known toxicity of lithium, it is not recommended as a rule in conjunction with radioiodine. Lithium alone has been to give lithium used to prepare patients for thyroidectomy (21, 22). This treatment resulted in decreasing in serum thyroid hormone concentrations and clinical improvement. When patients with thyroid cancer are treated with 131I, it is sometimes helpful to increase retention of the isotope by cancer tissue (23, 24). Lithium can prolong 131I retention by thyroid tissue. In one study of 15 patients who had diagnostic 131I scans before and then again after receiving lithium for one to two days, 131I retention was higher and more prolonged during lithium administration in metastatic lesions and the thyroid remnants in most patients, so that the estimated 131I dose to the metastases was higher. Whether these findings will result in improved eradication of metastases remains to be determined. In a study of 12 patients with metastatic differentiated thyroid cancer who had previously received radioiodine therapy without lithium, and who did not have a response despite radioiodine accumulation in metastases, treatment with lithium immediately prior to another dose of radioiodine did not have any beneficial effects on the clinical course assessed by thyroglobulin levels and radiographs. In the absence of clinical trial data showing a beneficial effect the American Thyroid Association clinical practice guideline does not suggest using lithium as an adjunct to radioiodine therapy (26).

CONCLUSIONS AND RECOMMENDATIONS

Lithium inhibits release of T4 and T3 from the thyroid gland, increases intrathyroidal iodine content, inhibits the coupling of iodotyrosine residues to thyroidine and triiodothyronine. Lithium can cause goiter and hypothyroidism, and its use has been associated with both thyroid autoimmunity and hyperthyroidism. Goiter and hypothyroidism are more common, occurring in approximately 40-50 and 20-30%, respectively, of patients treated with lithium. Because of the high incidence of thyroid dysfunction that occurs during lithium treatment, patients should have a careful thyroid physical examination and determination of serum TSH and antithyroid peroxidase antibody titers or ultrasonography of the thyroid gland before lithium treatment is introduced. Patients with normal thyroid function basic should be reevaluated every 6 to 12 months for several years, and thyroid dysfunction should be treated if diagnosed. The development of thyroid dysfunction does not typically require discontinuation of lithium. If thyroid function is abnormal at the initial evaluation, lithium can still be given if necessary, but the thyroid dysfunction should be treated. Because of its ability to inhibit thyroid secretion, lithium has been used in the treatment of several thyroid diseases. However, it is not used as a first-line therapy because of side effects and the availability of other antithyroid drugs. The side effects and potential organ toxicity require clinical and laboratory monitoring of lithium treated patients.
26. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer, Thyroid 2016; 26: 1.