Lithium Therapy and Thyroid Disorders

Keywords: Thyroid hormone release; Wnt/β-catenin signaling; Tyrosine kinase

Introduction

Lithium carbonate is used as a first-line treatment for bipolar disorder and is given to approximately 1 in every 200 patients with this psychiatric disease. Lithium, an element in the alkali metal group, has a variety of anti-thyroid effects, primarily goiter formation and hypothyroidism. Rarely, lithium may cause hyperthyroidism secondary to thyroiditis or through possible autoimmune actions. Since this cation can inhibit thyroid hormone release and increase retention of radioactive iodine, it can be used as an adjunct therapy in the treatment of hyperthyroidism and thyroid cancer. There are many proposed mechanisms for lithium's actions on thyroid hormone secretion, thyrocyte proliferation, and effects on the immune system, but more research is still required. We will review the pathophysiological mechanisms and clinical manifestations of lithium therapy on the thyroid gland.

Pathophysiology

Lithium inhibits the coupling of iodotyrosine residues in the formation of thyroxine (T4) and triiodothyronine (T3) [1], and the subsequent release of these iodotyrosines. Although the precise mechanism for this process is still uncertain, it may decrease the pinocytosis of colloid from the follicular lumen, leading to inhibition of colloid droplet formation [2] as well as the blockade of cellular events mediated by cyclic adenosine monophosphate (cAMP), either by directly inhibiting adenyl cyclase as a substitute for cationic enzymatic co-factors (e.g. Na+ or K+), or through the blockade of cAMP at any step in the cellular microenvironment [3]. Lithium may affect deiodinase activity, which is a group of enzymes that can either activate thyroid hormones by promoting the conversion of T4 to T3, or inactivate hormones by converting either T4 to reverse triiodothyronine (rT3) or T3 to inactive diiodothyronine (T2) [4]. Particularly, lithium has been shown to inhibit the type II deiodinase enzyme (5'-monodeiodinase), which is responsible for the peripheral conversion of T4 to T3 [5].

In addition, lithium can increase intrathyroidal iodine content [6], which inhibits the release of T4 and T3 through a feedback mechanism. The inhibition of organic iodine formation and inhibition of thyroid hormone secretion is responsible for the initial fall in serum T4 and T3 within hours of iodide therapy [7]. Since lithium inhibits iodine release from thyroid tissue without impairing iodine uptake, it can enhance the retention radioactive iodine (e.g. I-131) in normal thyroid and thyroid cancer cells [8], which may have treatment benefits and will be discussed later.

Since lithium is also concentrated in the pituitary gland and hypothalamus [9], there may be an effect on the hypothalamic-pituitary axis (HPA). Lithium-treated patients have been shown to demonstrate transient increases in both basal TSH and thyrotropin releasing hormone (TRH)-stimulated TSH levels [10-12], with the latter suggesting a direct effect on the HPA, rather than a feedback mechanism in response to decreased thyroid hormone secretion. Since many of these patients do not demonstrate low thyroid hormone levels, a reflex increase in TSH would not be expected.

Goiter

The most common thyroid abnormality associated with lithium treatment is goiter. The incidence is estimated to be 40 to 50% of patients treated with lithium [13-15], with a bias on gender, duration of treatment, and geographical location, which is likely related to dietary iodine content. When goiter formation occurs, it usually happens within the first two years of lithium treatment. Different from the direct effects on the HPA, the proposed method by which lithium induces goiter formation is thought to be through a compensatory increase in pituitary secretion of TSH from inhibition of thyroid hormone secretion by lithium, resulting in increased thyrocyte proliferation and normal thyroid hormone output [6,16]. Furthermore, other studies have demonstrated that lithium induces cellular proliferation through direct stimulation of DNA synthesis [17], activation of Wnt/β-catenin signaling [18], tyrosine kinase activation [19] and triggering a cascade of G-proteins coupled to IGF-1 receptors during the G1 phase of the cell cycle [20].
The goiter of a patient on lithium is usually twice the size of a normal thyroid gland and more likely to be diffusing than multinodular [21]. If present, the nodules in these goiters tend to regress over time. Histologically, the lithium-induced goiters demonstrate follicles with prominent epithelial cell pleomorphism and pronounced nuclear changes [22]. In a study that used ultrasound to measure thyroid gland sizes in bipolar patients, abnormally increased thyroid gland volumes were found in 44% of the patients who were treated with lithium for 1-5 years, 50% in patients treated over 10 years, but only 16% in those who have never received lithium [15]. Similarly, Bauer et al. [23] found that the total thyroid volume and clinical goiter evaluated by ultrasound was significantly greater in the lithium-treated group than among controls, and they recommended that sonographic evaluation of thyroid enlargement should be done routinely in patients on long-term lithium therapy [23].

As with goiters caused by other etiologies, treatment with levothyroxine may stop progression of thyroid gland enlargement [24]. However, since suppressive therapy with T4 may result in subclinical hyperthyroidism, patients are at increased risk for thyrotoxicosis, and in those with co-morbidities such as anxiety, atrial fibrillation, or reduced bone density; they may experience an exacerbation of symptoms or worsening of their disease [25]. In rare cases, the goiter may become large enough to cause obstruction or significant cosmetic concerns, warranting surgical treatment. Radioiodine therapy with I-131 is infrequently used in the United States, but is available as an option for those who develop compressive symptoms or who desire treatment for cosmetics but are unable to undergo surgery.

**Hypothyroidism**

Hypothyroidism is the next most common thyroid disorder associated with lithium therapy. Although it is usually subclinical and only found with elevated serum TSH levels, some patients are symptomatic. In either case, the treatment is the same with thyroid hormone supplementation as with other cases of hypothyroidism. Hypothyroidism can occur alone or in the presence of a goiter, with goiter formation usually manifested during the first two years of lithium treatment [26].

The prevalence of hypothyroidism in lithium-treated patients has been reported to be approximately 20%, with a range of 6 – 52% [24,27]. The risk of hypothyroidism increases with age, and it is higher in women than in men. The highest risk group for developing hypothyroidism is women over 45 years old [27-29]. Lithium-induced hypothyroidism is also observed more frequently in patients with a history of thyroid gland damage, such as prior external beam radiation or previous iodine-131 therapy. Additionally, the overabundance of iodine may also be a risk factor since iodine has been shown to have synergistic effects with lithium to cause hypothyroidism [30]. This effect may have clinical significance in patients who have immigrated from iodine-depleted to iodine-rich areas and are subsequently started on long-term lithium treatment.

Some of the patients who develop hypothyroidism may already have an underlying autoimmune thyroid disorder, with the presence of antithyroid antibodies prior to the commencement of lithium therapy. Studies have shown that the majority of patients who developed hypothyroidism after lithium therapy have either thyroid peroxidase antibodies and/or an exaggerated stimulation of TSH [21,31,32]. Other studies showed fluctuations in antibody titers over the course of lithium treatment, negating the possibility that lithium increases these antibodies [33]. It has also been suggested that the presence of TPO antibodies is more prevalent in bipolar patients than in control subjects, dismissing the notion that lithium may induce thyroid autoimmunity [34].

If the patient develops hypothyroidism on lithium therapy, thyroid hormone replacement with levothyroxine should be started, as in other etiologies of clinical hypothyroidism, with the goal to restore a euthyroid state. Contrary to treatment of much other drug-induced toxicity, discontinuation of lithium or alteration of dose is not advised.

**Hyperthyroidism**

On the other end of the spectrum of thyroid disorders, lithium treatment can also cause hyperthyroidism, although much less frequently. Nevertheless, the prevalence of lithium-induced hyperthyroidism is estimated to be 2-3 times greater than the general population [35,36]. Thyrotoxicosis associated with lithium has been reported to have an incidence of 2-7 cases per 1000 person-years, whereas lithium-induced silent thyroiditis has been reported to be around 1-3 cases per 1000 person-years, compared to the general population incidence of 0.8–1.2 and 0.03–0.28, respectively [36]. Various manifestations of lithium-induced hyperthyroidism have been described. Authors of one study determined that out of 13 lithium-treated patients, 8 had Graves’ disease, 2 toxic multinodular goiters, 1 toxic unilodular goiter, and 2 had silent thyroiditis [35]. It is unclear whether these patients classified as Graves’ disease were tested for TSH-receptor stimulating antibody or as a result from destructive granulomatous thyroiditis, with the latter being consistent with the histological findings in lithium-treated hyperthyroid patients described by Sinit et al. [37]. Wilson et al. [32] demonstrated that lithium could induce autoimmunity. They found that 20% of lithium-treated patients had anti-thyroid antibodies compared to only 7.5% in the 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.

Radioactive iodine uptake scans with iodine-123 or technetium-99m pertechnetate may be useful in the evaluation of lithium-treated patients with hyperthyroidism [35]. A low uptake will be seen in destructive lymphocytic or granulomatous thyroiditis, while a high uptake would be expected in other causes of hyperthyroidism. This differentiation will be useful in treatment decisions, as low uptake will preclude iodine-131 therapy.

The management of these hyperthyroid conditions should be tailored to the individual presentation, regardless of whether or not there was an association with lithium. This usually includes symptomatic treatment such as beta-blockers and antithyroid medications such as thionamides including methimazole and propylthiouracil (PTU). Radioiodine-131 therapy is a widely used treatment modality in the United States. Although radioiodine can be used as initial therapy, many older patients and those with comorbidities are usually first treated with antithyroid medications. Surgery can be used as a last resort for patients with large, obstructive goiters, in pregnant patients who are allergic to antithyroid medication and for those who are reluctant to undergo or refractory to radioiodine therapy. In patients with lithium-induced thyroiditis, conservative management with close follow-up is recommended.

**Lithium as a Therapeutic**

Despite the aforementioned association with hyperthyroidism, lithium’s ability to inhibit thyroid secretion has been exploited for treatment purposes. When indicated, a dose of 600 to 1000 mg/day can be an effective therapy for hyperthyroidism. The antithyroid
mechanism of action may be similar to that of iodine. After 10 days of lithium therapy, a reduction in serum-thyroxine iodine (T4I) by 27.0% and in free-thyroxine index (FTI) by 38.1% has been reported [38]. Others have shown that lithium caused a drop of over 40% in free T4 levels and clinical improvement was achieved in all but one patient (12/13) with 1 to 5 weeks of therapy [39]. Because of the significant side effects and possible exacerbation of thyrotoxicosis, lithium should not be used as a first-line therapy but should be reserved for patients who are refractory or resistant to thionamide medications (e.g. methimazole and propylthiouracil) or have an iodine allergy.

Radioactive Iodine-131 Therapy Adjunct

Due to the potential to prolong the retention of intrathyroidal iodine [40], lithium can potentially increase the efficacy in radioiodine treatment of hyperthyroid patients. It has been estimated that lithium can prolong the effective half-life of iodine-131 by 50%, which can lower the administered dose while maintaining the effective dose [41]. In addition, the concomitant administration of lithium with iodine-131 can prevent the transient increase in serum T4 concentrations following radioiodine therapy as can result in a radioiodine-damaged thyroid gland [42]. This effect can make iodine-131 therapy safer in certain patient populations, such as elderly patients and those with cardiovascular disease [43], by preventing a thyroid storm. Bogazzi et al. [44] determined that in patients who were given lithium (900 mg/day x 12 days) starting five days prior to iodine-131 therapy, there was a higher cure rate than those treated with radioactive iodine alone [44]. However, a previous randomized trial of radioiodine alone versus radioiodine plus 900 mg of daily lithium demonstrated no significant differences between the two groups [45]. Other authors report that the use of chronic lithium may reduce radioiodine uptake through an unknown mechanism [24]. Because of conflicting data and the associated toxicity, the use of lithium is cautioned in conjunction with radioiodine therapy.

Many thyroid cancer patients are treated with radioactive iodine. Whether for thyroid remnant ablation or treatment of metastatic disease, the dosimetry will be enhanced with an increase in retention of the radioiodine within the thyroid cells. Authors of one study in which 15 patients had two diagnostic iodine-131 scans (1.5 mCi/55.5 MBq), one before and another after receiving lithium for 1-2 days, found that the dosimetry demonstrated higher retention in thyroid remnants and/or metastatic lesions in patients taking lithium [41]. These patients could receive uptake to a twofold higher dose to their target lesions, particularly in the tumors that rapidly clear iodine. It is yet to be determined whether or not these observations will result in improved control of disease and significantly alter prognosis or disease-free survival. A more recent study of 12 patients with metastatic differentiated thyroid cancer who were administered lithium immediately prior to a re-treatment with iodine-131 failed to demonstrate beneficial clinical outcomes based on thyroglobulin levels and radiographic findings despite evidence of increased radioactive iodine in the tumor deposits [46]. Barbaro et al. [47] demonstrated that the administration of furosemide and lithium can cause a reduction in the circulating iodine pool, an increase in thyroidal uptake and retention of I-131, thereby improving recombinant TSH-stimulated I-131 ablation in patients with differentiated thyroid cancer [47]. Because of the limited data, the American Thyroid Association (ATA) revised thyroid cancer guidelines to neither recommend nor advise against the use of lithium as an adjunct to iodine-131 therapy [48].

Conclusion

Lithium can cause a spectrum of thyroid disorders, from hypothyroidism to hyperthyroidism through mechanisms that are not entirely understood. Due to the high incidence of these disorders in bipolar patients on lithium therapy, routine thyroid evaluation is important. All manic-depressive patients prior to initiating lithium therapy should undergo a thorough physical examination and laboratory evaluation, including a baseline serum thyroid stimulating hormone (TSH) and free T4 levels. These patients should be reevaluated periodically over the course of their treatment. If a lithium-induced thyroid disorder develops, appropriate treatment can be initiated without the need to discontinue or alter the dose of lithium. The role of lithium for treating hyperthyroidism or as an adjunct therapy in radioactive iodine treatment is still under discussion, and more data is needed to determine its role in patient management.

References


