

Lithium Treatment and Thyroid Disorders

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Abstract

Lithium is a widely used and effective long term therapy for bipolar disorders. Its use is associated with thyroid abnormalities commonly reported in the literature. Lithium affects normal functioning through multiple mechanisms. It inhibits synthesis and release of thyroid hormones and may reduce the thyroid iodine uptake. Lithium can induce thyrocyte proliferation by two mechanisms: the inhibition of the TSH/cAMP pathway and more recently identified is the activation of the Wnt/beta-catenin signaling pathway. Lithium finally affects different parameters of the immune system. Goitre is the most frequent disorder noted in up to 55% of patients on lithium therapy. Hypothyroidism is observed in up to 52%. Lithium induced hyperthyroidism is a less common and controversial finding. Lithium increases thyroid autoimmunity if present before therapy. Patients taking lithium should not stop the drug if thyroid dysfunction develops. Practicing clinicians managing lithium treated patients should be aware of these potential disorders. Adequate monitoring is essential in order to identify them and thus institute early and appropriate treatment.

Keywords: Hypothyroidism; Hyperthyroidism; Lithium; goitre

Introduction

Lithium was first discovered as a chemical element in 1817. By the mid-1800s, there was great interest in "urate imbalances", which were thought to explain a variety of diseases, including mania and depression. Around this time, it was discovered that a solution of lithium carbonate could dissolve stones made of urate. The first recorded use of lithium for the treatment of mania, based in part on the urate/lithium connection, was 1871. Use of lithium carbonate which is the current pill form of lithium to prevent depression came in 1886 [1].

Currently, lithium salts are used to treat mania, refractory and recurrent depression and bipolar disorders [2]. Despite recent advances in pharmacological treatment of psychiatric disorders, lithium remains an effective and inexpensive long-term therapy for bipolar disorders [3]. Although efficacious, lithium treatment is associated with a variety of adverse effects, mainly hypothyroidism, nephrogenic diabetes insipidus and hyperparathyroidism [4,5]. This review article will discuss the main thyroid disorders associated with lithium treatment.

Pharmacology of lithium

A number of salts of lithium are available in immediate and sustained release compounds. After an oral dose, lithium peak plasma concentrations are reached in 1-2 and 4-5 hours for the immediate and sustained release formulations respectively. Once absorbed, lithium reaches the extracellular fluid and gradually accumulates in the tissues. Because it is low protein bound, it is freely filtered by the kidneys and its excretion is dependent on glomerular filtration rate [6]. About 95% of the ingested dose is excreted in the urine without undergoing biotransformation. Its elimination half-life is 18-36 hours and may be longer with increasing age [6,7].

Lithium has a narrow therapeutic range; therefore, it is very important to monitor its plasma concentrations in patients under treatment. The oral dose of lithium and the plasma concentrations achieved are of fundamental importance to ensure both optimum efficacy and adequate tolerability [8]. The therapeutic serum concentrations of lithium are reasonably well defined (0.4-0.8 mmol/L). Concentrations greater than 0.6 mmol/L are necessary for acute mania, whereas lower plasma concentrations that might provide adequate depression prophylaxis and reduce the risks of long-term toxicity might not optimally reduce the recurrence of mania [9,10]. Toxic reactions appear as a result of elevated tissue concentrations [11].

Although lithium's therapeutic mechanisms are not fully understood, substantial *in vitro* and *in vivo* evidence suggests that it has neuroprotective/neurotrophic properties against various insults. Main lithium's mechanisms of action are inhibition of glycogen synthase kinase-3 and induction of brain-derived neurotrophic factor-mediated signaling, leading to enhanced cell survival pathways and alteration of a wide variety of downstream effectors. Lithium also inhibits the N-methyl-D-aspartate receptor-mediated calcium influx, contributing to calcium homeostasis and suppressing calcium-dependent activation of pro-apoptotic signaling pathways. In addition, lithium decreases inositol 1,4,5-trisphosphate by inhibiting phosphoinositol phosphatases, a process recently identified as a novel mechanism for inducing autophagy [12]. Lithium also modulates release of neurotransmitters, and decreases glutamatergic activity contributing to neuroprotection [13].

Effects on thyroid physiology

Lithium accumulates in thyroid tissue against a concentration gradient, by active transport. In treated patients, it induces structural and functional disturbances of the thyroid gland. Lithium interferes with thyroid hormones synthesis at two levels:

Thyroid iodine uptake: In rats, lithium reduces radioiodine uptake into thyroid and salivary glands *in-vivo* and *in-vitro*. The effects are different in humans where lithium administration has been reported to result in both a reduced as well as an increase in thyroidal radioiodine. The possible mechanisms for this are that lithium may compete for iodide transport resulting in low thyroid iodine uptake; it also causes iodide retention, the increase in uptake may also be due to thyroid-stimulating hormone (TSH) secreted as a result of lithium-induced hypothyroidism [14].

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Intra-Thyroidal Metabolism: The main thyroïdal action of lithium is to inhibit thyroid hormone synthesis and release. Lithium exerts this effect by altering the tubulin polymerisation and inhibiting the action of TSH on cyclic adenosine mono phosphate (c-AMP). It inhibits iodotyrosine coupling, alters thyroglobulin structure, and colloid formation. The ion decreases the activity of type I 5' de-iodinase enzyme reducing the clearance of free T4 [14,15]. It also inhibits deiodinase II, leading to a decrease in T3 pituitary concentrations [16]. It may result in increased TSH concentrations and hyper-response of TSH to throtropin-releasing hormone (TRH) [17]. The goitrogenic effect of lithium was observed early after its introduction in the treatment of maniac depression [18]. Two mechanisms are involved in lithium induced thyrocyte proliferation.

The first mechanism described is the inhibitory effect of lithium on the TSH/cAMP/cAMP response element binding protein (CREB) pathway [19,20]. The second mechanism more recently described implies the Wnt/beta-catenin signaling pathway [21]. By inhibiting GSK3B (glycogen synthase kinase B), an enzyme that degrades beta-catenin, lithium can simulate a functional activation of this molecular signaling pathway, which has a functional relevance for the regulation of thyroid cell proliferation, as an alternative to the cAMP pathway. Lithium finally affects different parameters of the immune system. Lithium treatment in patients with primary affective disorders increased B cell activity and decreased ratios of suppressor to cytotoxic T cells [22].

Thyroid Abnormalities due to Lithium Treatment and their Management

Goitre

Thyroid enlargement has been described early in patients receiving lithium for maniac depression [23]. Prevalences of goitre were very different in the various reported studies [14]. Differences in the methods of detection, the geographical origin of patients, especially related to iodine intake and duration of lithium treatment, are perhaps the main reasons for such discrepancies [15]. Schou et al. in 1968 reported occurrence of goitre in 12 out of 330 manic-depressive patients treated with lithium. The calculated incidence of goitre was 4% per year per 100 patients compared to a 1% incidence in the general population of a separate matched community [23]. Bocchetta et al. reported a 51% prevalence of clinically detected goitre in 150 patients receiving long-term lithium treatment [24]. A prevalence that decreased during follow up [25].

Large long-term prospective studies using reliable methods of detection, such as ultrasonic scans, are lacking. The most reliable existing study of goitre in maniac-depressive patients receiving long term lithium treatment, though cross-sectional, is perhaps that by Perrild et al. [26]. Ultrasonically determined thyroid size was larger than expected, according to age and weight of subjects, among patients treated with lithium for 1-5 years (44%) or more than 10 years (50%) than in patients who had never received lithium (16%). In a similar study in Germany, among 96 treated patients with affective disorders, goitre was reported among 53 (55%) patients on lithium therapy and 19 (20%) controls ($p=0.003$) [27]. In this study, screening using thyroid ultrasonography identified more patients with goitre compared to clinical palpation ($p<0.001$). The prevalence of goiter was higher in female patients, patients using the medication for long periods, those living in iodine-deficient areas [24,26], and smoking patients [26]. Clinically, the goitre is smooth and hard. It may develop within weeks of starting lithium therapy or may take months to years of lithium

treatment before diagnosis [28]. Management of patients on lithium therapy diagnosed with goitre is the same to that of any patient with goitre. As diffuse enlargement suggests the aetiological nature of lithium, recent signs of nodule enlargement or an irregularly shaped thyroid gland, must be appropriately investigated as the goitre may not be due to lithium therapy. In this situation, fine-needle aspiration cytology is recommended. Levothyroxine treatment is preferred in patients with significant thyroid enlargement especially if it is associated with neck compression symptoms. The dosage of Levothyroxine should be such that the TSH is not totally suppressed and the serum T4 and T3 concentrations are within normal limits [15].

Hypothyroidism

Hypothyroidism, irrespective of association with goitre, has been one of the main concerns regarding lithium treatment since the early 1970s [29]. The clinical presentation of hypothyroidism in lithium-treated patients is not different from that seen in other causes of hypothyroidism [15]. Sub-clinical hypothyroidism should be considered in a patient with poor response to lithium. Symptoms of the condition may appear within weeks, many months or even years of starting lithium [28] and may include the unusual or atypical features such as myxedema coma [30]. The prevalence of lithium-induced hypothyroidism and subclinical hypothyroidism varies widely from 0 to 52% [15] according to the population studied and the differences in clinical and laboratory evaluation [31]. In a review of 16 reports totalling 4681 patients up to 1986, the prevalence was 3.4% (range: 0-23.3%) [32]. Johnston and Eagles in a retrospective study of 718 lithium treated patients [33], found a 10.4% prevalence of clinical hypothyroidism. They identified a higher risk in women, especially those starting lithium in middle age (hypothyroidism prevalence >20%). They calculated retrospectively annual incidences 2.17% in women and 0.68% in men, which were substantially higher than the community incidences of hypothyroidism in the Whickham survey (0.41% and 0.06% respectively) [34]. Kirov et al. published a study of thyroid disorders in 274 long-term lithium treated patients. The prevalence of hypothyroidism was 10.3%; 17% in female patients and 3.5% in male patients, this prevalence increased in women over the age of 50 [35]. McKnight et al. recently published a meta-analysis of the more common adverse effects of lithium [5]. They identified 77 studies that reported the effects of lithium on thyroid function: 4 randomized controlled trials, 16 case-control studies, 15 cohort studies, 20 cross-sectional reports and 22 case reports. Because the randomized controlled trials collected heterogeneous data and the cohorts were uncontrolled, only the case-control studies were used for analysis. Also, studies before 1980 reported measures incompatible with more recent studies and therefore were not used for analysis. Meta-analysis showed more hypothyroidism in patients given lithium than in controls. The relative risk increased when only cases of clinical hypothyroidism were included ($p<0.0001$). TSH level was increased on average by 4.00 iU/mL ($p<0.0001$). The main limitations of this study were the quality and the quantity of the primary evidence. High-quality data from long-term randomized or controlled cohort studies were sparse, and the sample size of most included observational studies was quite small. Finally, some informations such timing of onset of side-effects in relation to the start of lithium and the concentrations of lithium in plasma were not precised. The aetiology of lithium associated hypothyroidism is related to the inhibition of thyroid hormone secretion and may occur in those with or without goiter [15]. In early reports of lithium-associated hypothyroidism, the presence of thyroid anti-microsomal antibodies was noted [15,32]. Lithium can accelerate the development of existing thyroiditis as demonstrated by lithium induced increase in thyroid antibody titre in patients who already were

antibody positive prior to lithium treatment [22,36]. Thyroid biopsies in some patients treated by lithium showed evidence of autoimmune thyroiditis [32]. Bocchetta et al. found a higher prevalence of subclinical hypothyroidism in patients receiving long-term lithium treatment who were thyroid antibody positive compared to negative antibody patients. They noted a positive correlation between the prevalence of thyroid antibodies and age, duration of lithium treatment, and female gender [24]. Cross-sectional studies have shown contrasting results about the higher prevalence of thyroid antibodies in lithium-treated patients compared with control populations [32,37]. Demonstrated risk factors of developing hypothyroidism in lithium treated patients were: female gender, age more than 50 years, family history of thyroid disease and presence of thyroid auto-antibodies [25,31,38]. When hypothyroidism is diagnosed in a patient receiving lithium, this treatment should not be stopped or the dose modified unless the serum level is outside the therapeutic range. Levothyroxine replacement therapy must be administered concurrently with lithium treatment, even in the presence of subclinical hypothyroidism [15,39].

Hyperthyroidism

Lithium induced thyrotoxicosis has been described since 1976 [40], however it is less commonly reported compared to goiter and hypothyroidism [35,41-45]. There are conflicting opinions regarding the relevance of hyperthyroidism during lithium treatment. Kirov et al. in their retrospective study in 209 long-term lithium treated patients, noted lithium induced thyrotoxicosis in 2 patients [41]. In this study the question arised was whether the reported higher rate of thyrotoxicosis in lithium-treated patients might reflect only a higher rate of this disorder in patients with affective disorders, and not a direct effect of lithium. This was supported by the increased rate of pre-lithium thyrotoxicosis in this sample noted in six female patients, a rate of 4.9%. McDermott et al. in 1986 reviewed 24 reported cases of thyrotoxicosis in lithium treated patients [46]. Considering the large number of patients treated with lithium, this small number of reported cases of hyperthyroidism might also simply represent the expected incidence in this population. In the prospective study by Kirov et al., in 57 patients (33 females, 24 males) followed-up between 1 and 7 years, hyperthyroidism was noted in one woman only [35] and was considered a very low frequency. Bocchetta et al. in their prospective study of 150 long-term lithium treated patients followed-up for 15 years, observed 1 case of thyrotoxicosis, corresponding to an annual rate of 0.1% similar to the incidence reported in the general female population [45]. In the meta-analysis of McKnight et al., there was no evidence of elevated prevalence of thyrotoxicosis among patients treated by lithium compared to controls [5]. Conversely, Barclay et al. [43] reported 14 cases and calculated retrospectively a higher than expected incidence of hyperthyroidism. The aetiology of hyperthyroidism associated with lithium treatment included Graves' disease, toxic nodular goiter, granulomatous thyroiditis and silent thyroiditis [22,47,48]. A large retrospective review demonstrated that lithium-associated silent thyroiditis and thyrotoxicosis had a much higher incidence (1.3 and 2.7 cases per 1000 person years, respectively) than that seen in the general population (0.03-0.28 and 0.8-1.2, respectively) [49]. A direct toxicity of lithium on thyroid cells may explain this silent thyroiditis [15,49]. Autoimmune hyperthyroidism is controversial in the pathogenesis of lithium-induced thyrotoxicosis. Nine of the 14 patients in the series of Barclay et al., had autoimmune thyrotoxicosis [43]. There is no information on the propensity of lithium to increase the titre of TSH-receptor-stimulating antibody in a manner similar to its action on anti-TPO antibody. As Graves' disease is common, at least in women, the chance of development of this condition in women

receiving lithium therapy can be expected [15]. Patients with lithium induced hyperthyroidism are best treated with anti thyroid drugs with/without steroids. Radioiodine or thyroidectomy should be reserved for patients with lithium induced Graves' disease especially in cases of poor compliance to the anti-thyroid drugs. In cases of a toxic nodular goitre, surgical resection is required, especially in the presence of compressive neck symptoms. The radioiodine uptake will be low in the cases of thyroiditis, thus excluding the use of radioiodine therapy. In these cases, a simple follow-up is recommended because of the common spontaneous evolution to hypothyroidism [48].

In summary, it's actually well established that lithium treatment is associated with thyroid abnormalities. However, thyroid disorders have been found in excess among patients suffering from mood disorders irrespective of lithium exposure. Kupka et al. demonstrated that the prevalence of autoimmune thyroiditis was higher in bipolar patients than in population and psychiatric controls, without association with lithium treatment [50]. Ozsoy S et al. in their cross-sectional and longitudinal study found a higher thyroid volume, lower thyroid hormone levels and higher TSH levels in lithium naïve patients with bipolar disorders than in controls, and in long term lithium-treated patients compared to lithium naïve patients. After lithium treatment, FT3 levels were lower, TSH levels were higher, and thyroid volume higher compared to those before lithium treatment [51].

Monitoring of Thyroid Function in Lithium Treated Patients

The UK National Institute for Health and Clinical Excellence guidelines recommended in 2006 to perform a thyroid function test at start of lithium therapy and every 6 months; more often if evidence of deterioration [52]. Thyroid function test is limited to measurement of TSH concentration [5,52]. Bocchetta and Loviselli in their review in 2006 [31], specified that assessment of thyroid function prior to starting lithium prophylaxis should include measurement of serum concentrations of TSH, FT3, FT4, anti-thyroperoxydase antibodies and ultrasonic scanning. A similar panel should be repeated at one year. Thereafter, annual measurements of TSH may be sufficient to prevent overt hypothyroidism. In the presence of subclinical hypothyroidism, shorter intervals between assessments are advisable (4-6 months). Measurement of anti-thyroperoxydase antibodies and ultrasonic scanning may be repeated at 2-to-3-year intervals. The patient must be referred to the endocrinologist if TSH concentrations are repeatedly abnormal, and/or goitre or nodules are detected [31]. Lazarus JH recommended in 2009 measurement of TSH, FT4 and TPO antibodies before starting lithium treatment, and regularly while on treatment [15].

Conclusion

Lithium is frequently used, as it is an effective and inexpensive medication in the treatment of bipolar disorders. Lithium causes goitre and hypothyroidism in a significant number of patients receiving the drug. It exacerbates pre-existing autoimmune thyroid disease by accelerating the increase in thyroid antibody titre. The presence of thyroid function abnormalities should not constitute an outright contraindication to lithium treatment. Similarly, lithium should not be stopped if a patient develops thyroid abnormalities. Thyroid disorders should be kept in mind of practicing clinicians managing lithium treated patients, to screen them clinically and by measurement of TSH level during follow-up in order to institute early and appropriate treatment.

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