LITHIUM AND ENDOCRINE DYSFUNCTION

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Abstract
Lithium carbonate is a commonly prescribed drug for bipolar disorders. In addition to its action on the central nervous system, lithium has systemic effects on multiple organs such as kidney, heart, motor end plate, thyroid and parathyroid glands. It can cause hypothyroidism, hyperthyroidism, goiter and ophthalmopathy by different mechanisms. It increases intrathyroid iodine content or compete for iodine transport, resulting in low iodine uptake by the thyroid. It also inhibits the coupling of iodotyrosine residues to form iodothyronines and inhibits the release of T4 and T3. Lithium has direct actions on parathyroid glands by antagonizing the calcium sensing receptor, which may induce hypercalcemia or even hyperparathyroidism, requiring surgery in some cases. Furthermore, it inhibits the expression of aquaporins, mainly aquaporin 2, in the renal collecting tubule by unknown mechanisms leading to nephrogenic diabetes insipidus. This adverse effect is usually reversible after drug withdrawal. However, some patients may present irreversible kidney damage due to chronic interstitial nephropathy.

Key words: lithium, thyroid disorders, hypercalcemia, nephrogenic diabetes insipidus

Resumen
El carbonato de litio es un fármaco que se prescribe comúnmente para el tratamiento de trastornos bipolares. Además de su acción sobre el sistema nervioso central, el litio tiene repercusiones sistémicas, afectando a múltiples órganos como el riñón, el corazón, la placa motora terminal y glándulas tiroideas y paratiroides. Puede causar hipotiroidismo, hipertiroidismo, bocio y oftalmopatía por diferentes mecanismos; también aumentar el contenido de yodo intratiroideo o competir por el transporte de yodo, lo que resulta en una baja captación tiroidea de yodo. Inhibe el acoplamiento de residuos de yodotirosina para formar yodotironinas e inhibe la liberación de T4 y T3. Tiene acciones directas sobre las glándulas paratiroides antagonizando el receptor sensor de calcio, lo que puede inducir hipercalemia e incluso hiperparatiroidismo, y puede requerir cirugía en algunos casos. Inhibe la expresión de acuaporinas en el túbulo colector renal, principalmente aquaporina 2, por mecanismos que aún no se conocen, produciendo diabetes insípida nefrogénica; este efecto adverso suele ser reversible tras la suspensión del fármaco. Sin embargo, algunos pacientes pueden presentar daño renal irreversible por nefropatía intersticial crónica.

Palabras clave: litio, tiroideopatías, hipercalemia, diabetes insípida nefrogénica

KEY POINTS
- Lithium carbonate affects multiple organs such as kidney, heart, the motor endplate and thyroid and parathyroid glands.
- Thyroid disorders are the most common endocrine adverse effects of lithium therapy; including hypothyroidism, hyperthyroidism, goiter and ophthalmopathy.
- Lithium-induced hypercalcemia and hyperparathyroidism may sometimes require surgical treatment.
- Nephrogenic diabetes insipidus generally remits with discontinuation of the drug, although chronic renal failure can occur.
- A baseline biochemical study and periodic monitoring should always be carried out after the beginning of lithium therapy to prevent major complications.

Lithium carbonate is a psychotropic drug frequently prescribed as an antimanic drug, in the treatment of aggressive-impulsive behaviors and mainly in bipolar disorders. It is an inorganic salt formed by two lithium (Li+) cations and a carbonate anion (Li₂CO₃) (Fig. 1). It is also widely used in industry, such as manufacture of rechargeable batteries, electrical porcelain, coating of welding electrodes, glues, luminescent paints, varnishes and colorants.

In 1970, thirty years after the first description by John Cade, the Food and Drug Administration approved the use of lithium for the treatment of mania and the prevention of bipolar disorder relapse.

Lithium acts on multiple neurological circuits, causing an increase of acetylcholine concentration, synthesis and turnover in the cholinergic system and a decrease of dopamine and noradrenaline concentration, storage and release in the catecholaminergic system. It also produces...
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Lithium has many effects on thyroid physiology. It can cause hypothyroidism, hyperthyroidism, goiter and ophthalmopathy. These side effects are caused by different mechanisms.

Lithium accumulates in thyroid tissue by active transport and the concentration can be 3 to 4 times higher than in plasma. It increases intrathyroidal iodine content and this could be due to thyroid-stimulating hormone (TSH) secretion as a result of lithium-induced hypothyroidism. Furthermore, lithium may compete for iodine transport resulting in low thyroid iodine uptake, which is reversible and dose-dependent.

Lithium also inhibits the coupling of iodothyrosines to form iodothyronines and inhibits the release of T4 and T3, which is the main mechanism involved in hypothyroidism and goiter. The mechanism of hormone release inhibition involves an alteration in tubulin polymerization as well as inhibition of the action of TSH on cyclic adenosine monophosphate production. This cation reduces thyroid iodine uptake, interfering with tyrosine iodination, changing thyroglobulin structure and colloid formation in the apical pole of thyroid cells, thus interfering with iodotyrosine synthesis. Lithium decreases in vitro colloid droplet formation within thyroid follicular cells, a reflection of decreased colloid pinocytosis from the follicular lumen.

The significant decrease of plasma T4 clearance in patients receiving lithium may be due to inhibition of thyroid hormone secretion, thereby inducing a decrease of type 1' deiodinase activity (DIO1). It also inhibits type II deiodinase enzyme (DIO2), leading to a decrease in pituitary T3 concentrations.

**Goiter**

Up to 50% of patients on chronic lithium treatment may develop goiter. The prevalence of goiter is higher in long-term users and in those patients living in iodine-deficient areas. It is usually a diffuse, painless and benign goiter. The inhibition of thyroid hormone secretion by lithium results in decreased serum T4 and T3 concentrations, with a compensatory increase in pituitary secretion of TSH, leading to thyroid enlargement and secretion of a normal amount of thyroid hormone by an enlarged thyroid gland. Goiter occurs more frequently within the first two years of treatment.

Thyroid enlargement may also be due to insulin-like growth factor alterations induced by lithium, post-receptor tyrosine kinase pathway and/or Wnt/beta-catenin signaling.
The management should be the same as in any patient with goiter and it would be a good practice to perform a thyroid ultrasound before starting lithium.

**Hypothyroidism**

Up to 30% of patients chronically treated with lithium develop increased TSH that may progress to overt hypothyroidism. It usually occurs during the first two years of lithium therapy and is more frequent in women over 45 years old, with an increasing risk with age. It is reversible with the discontinuation of lithium.

If hypothyroidism develops, treatment with levothyroxine should be started. There is no need to stop treatment with lithium, but if lithium is subsequently discontinued, it is reasonable to reassess the need for continuing thyroid hormone replacement. Some guidelines suggest measuring TSH two months after withdrawal. If TSH is in the lower half of the normal range or below normal, levothyroxine should be discontinued and TSH and free T4 should be reassessed in six weeks. If TSH rises above normal, levothyroxine may be restarted, depending on free T4 level and clinical assessment. On the contrary, if the TSH is in the upper half of the normal range or above normal after lithium withdrawal, levothyroxine should be continued.

There is a strong recommendation for measuring thyroid function and antibodies in all patients prior to lithium therapy regardless of gender or age. Besides, it is reasonable to perform annual thyroid function tests in patients receiving lithium.

**Autoimmune thyroiditis**

It is not clear if lithium itself can induce autoimmunity. It is likely that many patients who develop hypothyroidism during lithium treatment have underlying chronic autoimmune thyroiditis. Some studies have shown that it can accelerate the development of preexisting thyroiditis. The drug does not seem to be able to stimulate the production of thyroid antibodies de novo, but there is evidence that lithium therapy is associated with a rise in antibody titer in patients who already have positive antibodies at the beginning of the treatment.

**Hyperthyroidism**

Hyperthyroidism is a rare complication of lithium treatment with an incidence range from 0.1-1.7% in patients treated with lithium, the frequency of hyperthyroidism was two to three times higher than in the general population.

One study proposes that lithium induced thyroiditis is a consequence of maladaptation to disturbed iodine kinetics with an escape phenomenon after expansion of the intrathyroidal iodine pool. In a review of 21 published cases of lithium induced thyroiditis, Lazarus concluded that besides an autoimmune mechanism, diffuse hyperplasia might be the main cause of this manifestation. Furthermore, lithium could cause direct damage to thyroid cells, with the consequent release of preformed hormones into the bloodstream; a mechanism similar to that of amiodarone-induced thyroiditis.
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The etiology of hyperthyroidism includes Graves’ disease, toxic nodular goiter and silent thyroiditis and should be accordingly treated.

**Ophthalmic adverse effects**

In patients taking lithium, thyroid eye disease is most commonly seen in hyperthyroidism, but it can also be seen in hypothyroidism and euthyroid state.

The most common signs and symptoms are eyelid retraction, exophthalmos, diplopia, ocular injection, lagophthalmos, dry eyes and vision loss.

Some patients develop exophthalmos even within therapeutic serum lithium range. The exophthalmos produced by lithium does not have the retroorbital infiltrative changes seen in Graves’ disease. Discontinuation of lithium leads to improvement of exophthalmos over the course of several months.

Further research is warranted to guide clinical decision-making in managing patients presenting with exophthalmos in the setting of lithium treatment.

**Treatment with lithium in thyroid disease**

Lithium has been used for many thyroid disorders, even though is not considered a first line treatment.

Hyperthyroidism: lithium can be used for the treatment of hyperthyroidism in doses between 600 to 1000 mg a day in patients allergic to iodine, with intolerance or lack of response to thionamides and in amiodarone induced thyrotoxicosis. This treatment leads to a decrease in serum thyroid hormone concentrations and clinical improvement. Thyroid cancer: as mentioned previously, lithium could lengthen iodine retention after radioiodine thus increasing its effectiveness. However, in the absence of clinical trials showing a beneficial effect, American Thyroid Association (ATA) does not suggest using lithium as an adjunct to radioiodine.

**Hypercalcemia and hyperparathyroidism**

The prevalence of lithium-induced hyperparathyroidism ranges from 6.3% to 50% in those patients who require long-term therapy and its incidence is higher in women (4:1). The prevalence is difficult to establish because it is undiagnosed in asymptomatic cases and because the assays employed to measure PTH or calcium vary in different studies.

According to a literature review, there have been published 84 cases since 1973, between 21 and 84 years. Among these patients, 42 had adenomas and 29 had diffuse parathyroid hyperplasia.

It has been shown that PTH increases 30%, calcium 2.5% and magnesium 5% with lithium treatment compared to their baseline values. These increases do not seem to be related to the duration of therapy, as cases have been reported in patients treated for only 4 weeks, nor have they been associated with the dose of lithium or derived from its toxicity.

**Pathogenesis**

Lithium has direct actions on parathyroid glands antagonizing the calcium sensing receptor (CaSR): it increases the calcium threshold necessary to decrease PTH secretion thus reducing the suppression of PTH by serum calcium. It remains to be elucidated whether the lithium ion binds directly to the CaSR or affects its function through a different mechanism. By shifting the PTH/calcium secretion curve to the right, higher serum calcium levels are required to inhibit PTH secretion, finally increasing both their levels.

It also has indirect actions promoting the reduction of urinary calcium excretion due to the increase in renal reabsorption secondary to PTH increase, and also causing an increase in intestinal calcium absorption.

Patients who develop lithium-induced hyperparathyroidism typically have serum calcium levels ranging from slightly above the normal range to more than 15 mg/dl and PTH levels ranging from high normal to several times the upper limit of normal. In cases where the PTH level is within the normal range, it is generally higher than would be expected for a given serum calcium level because the parathyroid glands normally respond to hypercalcemia by suppressing PTH secretion below the lower limit of reference. In lithium-associated hyperparathyroidism, renal cyclic AMP levels are low or normal, serum phosphate levels are usually in the normal range and serum magnesium levels are elevated. Unlike primary hyperparathyroidism, lithium-induced hyperparathyroidism is associated with hypocalciuria and, consequently, is less likely to present with kidney stones.

**Diagnosis and treatment**

Monitoring of calcium levels is recommended before starting lithium therapy and subsequent monitoring 2-6 weeks after starting it. After this initial follow-up, annual calcium
control is suggested for surveillance. If patients remain asymptomatic, biochemical control for calcium should be performed annually\(^\text{63}\).

Once confirmation of hyperparathyroidism is reached, in the absence of a lithium overdose, the clinician must then decide between three main options: cessation of lithium and consideration of alternative psychiatric medication(s), monitoring of calcium levels while remaining on lithium and parathyroid exploration and surgical excision of abnormal parathyroid tissue\(^\text{64}\).

Given the choice to discontinue lithium, a 28-fold higher mania relapse rate was reported 3 months later. In addition to the psychiatric consequences, there are still patients who will remain hypercalcemic after cessation of lithium therapy\(^\text{63}\).

If lithium therapy should still be continued, calcium, kidney function and bone mineral density should be monitored in all patients every 6-12 months. In selected cases the use of cinacalcet (allosteric activator of CaSR) could be an alternative to be considered\(^\text{65}\). This drug decreases the activation threshold of the CaSR by extracellular calcium and promotes a subsequent decrease in PTH secretion. To date, only five patients have been treated with cinacalcet with subsequent improvement of hypercalcemia during lithium therapy. No adverse effects have been reported and the therapy was well tolerated\(^\text{65, 66}\).

Surgery is indicated in all patients who cannot be cured or when lithium therapy discontinuation is not recommended. The approach is controversial because between 25% and 75% present with multiglandular pathology\(^\text{67, 68}\). Unilateral parathyroidectomy is recommended when preoperative location of the lesion has been possible and when intraoperative PTH measurement is available. In the absence of localization, bilateral exploration with removal only of the abnormal glands or subtotal parathyroidectomy (three and one half glands) is recommended\(^\text{64}\).

### Nephrogenic diabetes insipidus

The kidneys’ ability to retain water and concentrate urine is regulated by ADH, renal medulla osmolality, adequate sodium transport and aquaporins function\(^\text{69}\).

The use of lithium is the most common cause of acquired nephrogenic diabetes insipidus (NDI) and up to 20-40% of patients can develop it\(^\text{70}\). Its clinical presentation is gradual and is characterized by polyuria, polydipsia and low urinary osmolarity.

Aquaporins are water channels that are expressed in the renal tubules and collecting ducts. The greater the activation of aquaporins, the greater the reabsorption of water in the renal collecting ducts, which reduces the volume of urine. Lithium inhibits the expression of aquaporin channels in the renal collecting tubule, mainly aquaporin 2. The possible mechanisms proposed are the decrease in cAMP due to lower expression of the β isoform of the enzyme glycogen synthetase kinase or less transport of aquaporins towards the apical membranes\(^\text{6}\). This inhibition of aquaporins during lithium treatment produces polyuria\(^\text{70-72}\) (Fig. 3).

This adverse effect is usually reversible after drug withdrawal, however some patients may present irreversible kidney damage due to chronic interstitial nephropathy\(^\text{6, 73}\).

To prevent renal toxicity, in addition to monitoring serum lithium and creatinine levels, a single daily dose of lithium should be preferred\(^\text{73}\). Thiazide diuretics are a therapeutic option in NDI; however, hydrochlorothiazide has the potential to increase lithium toxicity and should be used with caution in these cases. Amiloride would be a better option because in addition to its natriuretic action (which causes the contraction of extracellular volume, the consequent decrease in glomerular filtration and ultimately leads to a decrease in urine volume), it also reduces the entry of urine lithium in distal tubule cells\(^\text{6, 74}\).

### TABLE 1.– Differences between primary hyperparathyroidism and lithium induced hyperparathyroidism

<table>
<thead>
<tr>
<th>Primary hyperparathyroidism</th>
<th>Lithium-induced hyperparathyroidism</th>
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</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Variable hypercalcemia</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Normal phosphatemia</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Hypocalciuria</td>
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<tr>
<td>Increased tubular reabsorption of calcium</td>
<td>Decreased urinary calcium excretion</td>
</tr>
<tr>
<td>Increased bone resorption</td>
<td>Reduced bone resorption</td>
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</table>
In conclusion, lithium therapy continues to be one of the most prescribed medications to treat bipolar disorders. However, the adverse effects induced by lithium over the endocrine system are quite common. Therefore, it is essential for physicians to know how to carry out a complete and adequate clinical and biochemical analysis for the early identification of these disorders. The withdrawal of lithium or its replacement by another treatment should be evaluated in the presence of endocrine dysfunction.

**Conflict of interest:** None to declare

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