Endocrine disturbances related to the use of lithium

Distúrbios endocrinológicos relacionados ao uso de lítio

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SUMMARY

Despite recent advances in pharmacological treatment of psychiatric disorders, lithium salts remain frequently used, as they are effective and inexpensive alternatives, especially in the treatment of bipolar disorders. Their use is commonly associated with various endocrine disorders, mainly in thyroid and parathyroid function, and in mineral metabolism. This article aims at reviewing these potential endocrinopathies related to the use of lithium to make health care professionals aware and familiar with these possible complications when they follow up patients using this drug, and to make them able to monitor, identify and institute early and appropriate treatment. Arq Bras Endocrinol Metab. 2012;56(3):153-8

Keywords

Lithium; hypercalcemia; *diabetes insipidus*; goiter

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SUMÁRIO

Apesar dos recentes avanços farmacológicos no tratamento dos transtornos psiquiátricos, os sais de lítio permanecem como uma alternativa eficaz e de menor custo, sendo usados com frequência principalmente no tratamento dos transtornos bipolares. O seu uso é comumente relacionado com diversas alterações endocrinológicas, principalmente nas funções tiroidiana, paratiroidiana e do metabolismo iônico. Este artigo tem por objetivo fazer uma revisão dessas potenciais endocrinopatias relacionadas ao uso do lítio, para que, no seguimento de pacientes em uso dessa medicação, os profissionais de saúde estejam atentos e familiarizados com essas possíveis complicações, conseguindo identificar e instituir tratamento precocemente. Arq Bras Endocrinol Metab. 2012;56(3):153-8

Descritores

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INTRODUCTION

Lithium salts were introduced into medical therapy in the mid-19th century, with reports of their use in migraine prophylaxis, and in the treatment of psychiatric disorders, gout and neutropenia (1,2). Currently, they are available in immediate- and extended-release formulas and are used to treat mania, refractory and recurrent depression and bipolar disorders with reduced morbidity and mortality. Despite recent advances in pharmacological treatment of psychiatric disorders, these salts remain effective and inexpensive alternatives (3,4).

Lithium can promote major endocrine and metabolic disturbances, mainly in thyroid and parathyroid functions, and in the mineral metabolism (5). This review article will discuss the main endocrine disorders related to the use of lithium salts.

PHARMACOLOGICAL ASPECTS

The exact mechanism by which lithium acts as a mood stabilizer is still unknown. Many molecular and cellular activities are involved in its neuroprotective and neurotropic properties. Due to an inhibition of the calcium-influx mediating receptor N-methyl D-aspartate, lithium interferes with calcium homeostasis and suppresses the activation of pro-apoptotic calcium-dependent signal-

ing pathways (6). It also seems to act in the modulation of neurotransmitters and reduce glutaminergic activity, contributing to neuroprotection. In addition, it modulates pathways that regulate neuronal plasticity, such as glycogen synthase kinase 3β, cAMP-dependent kinase and protein kinase C (7).

Because of lithium narrow therapeutic range and possible overdose potential, small elevations in its circulating levels may be associated with toxic reactions. Therefore, it is very important to monitor its plasma concentrations in patients under treatment. It is recommended that serum levels are assessed every 3-6 months (3). The therapeutic concentration that is considered safe ranges from 0.6-1.25 mEq/L but, when used for a long time, maximum levels of 0.75 mEq/L are preferable. The doses of lithium carbonate recommended to achieve this goal vary from 900 to 1,500 mg per day (1).

Lithium is absorbed rapidly and almost completely from the gastrointestinal tract. After an oral dose, absorption occurs in up to 8 hours and reaches its highest serum concentration in 2 to 4 hours. Slow-release preparations reduce the rate of absorption and therefore the peak plasma level. 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. About 95% of the ingested dose is excreted in the urine without undergoing biotransformation. Its half-life is up to 24 hours and may be longer in the elderly (1,3). Approximately 80% of lithium is reabsorbed in the proximal renal tubules. The administration of massive doses of sodium leads to greater lithium elimination, while states of sodium depletion lead to a greater retention, increasing the risk of intoxication (8).

At therapeutic doses, nausea, diarrhea, weight gain, fine tremor of the hands, and skin lesions, especially acne and psoriasis, may happen (9). The major toxic effects related to the use of lithium are the cognitive disturbances, dysarthria, and impaired coordination. The most severe effects include mental confusion, hyperreflexia, gross tremor, focal neurologic signs, seizures, coma, and even death (1,3). Other toxic effects include albuminuria, hypotension, and cardiac arrhythmias. Electrocardiographic alterations include prolongation of the QT interval, and changes in the ST segment and T wave (10).

DISTURBANCES IN THE ENDOCRINE SYSTEM

Mineral metabolism

Chronic use of lithium is generally associated with mild hypercalcemia, which is usually reversible with the withdrawal of the medication. However, in some cases, there may be persistent hypercalcemia, and even the development of hyperparathyroidism, by means of a still unknown mechanism (11).

The addition of lithium to parathyroid cells cultures (both normal and hyperplasic) causes an increase in PTH levels from 1.4 to 5.3 times. *In vivo*, several experiments demonstrated that lithium interferes with the dynamics of PTH secretion by increasing the setpoint of parathyroid calcium-sensing receptor. By shifting the PTH/calcium secretion curve to the right, higher levels of serum calcium are required to inhibit PTH secretion, thus increasing calcemia and PTH levels (12-14). Lithium also promotes reduced urinary excretion of calcium due to increased renal resorption secondary to PTH increase (15).

The prevalence of hyperparathyroidism associated with lithium is higher in women (4:1), with the occurrence of both parathyroid adenomas and hyperplasia. The best approach must be individually evaluated in each case since there is no exact recommendation on the best surgical procedure in these cases (16). As an alternative to surgery, especially in cases of persistent hyperparathyroidism, the use of calcium mimetic agent (Cinacalcet) has been reported with good results (17).

A recent review and meta-analysis about lithium toxicity profile recommends that calcium concentrations should always be checked before and during lithium treatment (18).

Thyroid

Some patients treated with lithium may develop thyroid enlargement. Induction of thyroid cell growth is reported even in ectopic thyroids (19). This goitrogenic potential can be manifested in up to 50% of patients taking lithium chronically. Generally, it is diffuse, painless, and benign goiter (20).

Concerning lithium interference with the regulation of thyroid cell proliferation, there are conflicting descriptions about its inhibitory effect on the cAMP pathway (21,22). Therefore, the Wnt/B-catenin pathway assumes an emerging role in these regulatory mechanisms. By inhibiting GSK3B (glycogen synthase

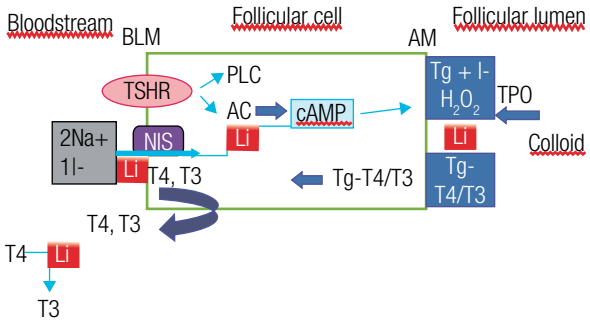
kinase B), an enzyme that degrades B-catenin, lithium can simulate a functional activation of this molecular signaling pathway, which has a functional relevance for the regulation of thyroid cell proliferation, as an alternative to the cAMP pathway (23).

Inhibition of the release of thyroid hormones is the main mechanism involved in hypothyroidism and goiter related to lithium use. It is unclear how patients who will develop goiter can be identified. Generally, women and patients with detectable thyroid antibodies before starting to use lithium are more likely to develop thyroid abnormalities. The prevalence of goiter is higher in patients using the medication for long periods and in those living in iodine-deficient areas. The interval between starting treatment and the onset of goiter may vary from a few weeks to several years. The risk of thyroid cancer is not increased in these patients (24-26).

The presence of autoimmune thyroiditis predisposes to hypothyroidism and goiter during treatment with lithium, with a relative risk of 8.4 compared with patients with negative antibodies (27). However, the exact role of autoimmunity in thyroid failure induced by the drug remains uncertain. In addition, there is controversy about the effects of the drug in inducing thyroid autoimmunity (28). Gland involvement may occur even in the absence of autoantibodies, showing that thyroid dysfunction can exist independently of the autoimmune process (29). Instead of inducing autoimmunity, lithium appears to stimulate secretion of immunoglobulins by lymphocytes, triggering a pre-existing immune response (28). Autoimmune thyroid disease precipitated by lithium also appears to be related to an interference with the function of CD8 suppressor cells (30).

Lithium accumulates in thyroid tissue against a concentration gradient, by active transport. This cation reduces iodine uptake by the thyroid gland, interfering with tyrosine iodination, changing thyroglobulin structure and colloid formation in the apical pole of thyroid cells, thus interfering with iodotyrosine synthesis (Figure 1). It also inhibits deiodinase 2, leading to a decrease in T3 pituitary concentrations (31). Treatment with lithium may also lead to a hyper-response of TSH in the TRH test (32). Up to 30% of patients chronically treated with lithium develop increased TSH (subclinical hypothyroidism) that may progress to overt hypothyroidism, with or without goiter (33).

Lithium inhibition of thyroid iodine uptake is reversible and dose-dependent (35). This inhibition is more pronounced in patients with hyperthyroidism.



BLM: basolateral membrane; AM: apical membrane; PLC: phospholipase C; AC: adenylate cyclase; cAMP: cyclic adenosine monophosphate; TPO: thyroperoxidase; Tg: thyroglobulin; T4: thyroxine; T3: triiodothyronine; Li: lithium; Na^+: sodium; I^-: iodide; NIS: sodium-iodide symport; TSHR: TSH receptor.

Figure 1. Main points involved in lithium-induced thyroid dysfunction. Adapted from: Williams Textbook of Endocrinology. 11th edition. 2008 (34).

Lithium in low doses is used as a therapeutic alternative in thyrotoxicosis patients who cannot tolerate or do not respond to thyonamides (36). Another therapeutic use is the association of lithium and radioactive iodine in the treatment of Graves' disease. Several series show that this association leads to a more rapid control of thyrotoxicosis, increasing therapeutic efficacy when compared with radioiodine alone, due to the inhibition of radioiodine release by the thyroid (37). Silent thyroiditis and thyrotoxicosis have been less frequently reported after long-term lithium use, possibly as a direct effect of the drug on follicular cells (38).

A rare report is the occurrence of Hashimoto's encephalopathy triggered by lithium, with increased antimicrossomal antibody titers in cerebrospinal fluid, reflecting the exposure the thyroid and central nervous system to common antigens (39).

Thyroid function, antithyroid antibodies and ultrasound of the gland are recommended before starting lithium therapy, with repeated screenings at regular intervals during treatment (26).

It is important to note that the presence of abnormalities in thyroid function is not an absolute contraindication to the use of lithium, neither its discontinuation is required in the eventual onset of thyroid disturbances during lithium treatment. The management of thyroid dysfunction can be done even with the maintenance of lithium therapy, but the risks and benefits of such approach always have to be assessed (26).

Nephrogenic *diabetes insipidus*

Arginine-vasopressin or antidiuretic hormone (ADH) is secreted by the hypothalamus, stored, and released by the posterior pituitary. This hormone plays a key role in the control of body fluids. Its signaling mechanism is mediated by G protein-coupled receptors and is directly related to increased intracellular cAMP.

The ability of the kidneys to retain water and concentrate urine is regulated by ADH, the osmolality of the renal medulla, appropriate sodium transport and the function of aquaporins (40). Aquaporins are water channels inside of proteins expressed in renal tubules and collecting ducts. The greater the activation of aquaporins, the greater water reabsorption in renal collecting ducts, reducing the volume of urine. When the expression of aquaporins is inhibited, polyuria ensues. Nephrogenic *diabetes insipidus* (NDI) is characterized by renal inability to concentrate urine, even in the presence of normal concentrations of ADH, causing a clinical polyuric syndrome.

The binding of the ADH to the V2 receptor stimulates the expression of aquaporins in the kidney (41). Lithium inhibits the expression of these aquaporins in the renal collecting duct, mainly aquaporin 2 (AQP2), by mechanisms still not fully understood (42). Most studies show an inhibition of adenylate cyclase activity (43). However it has already been demonstrated in animal models that lithium-induced downregulation of AQP2 is independent of cAMP and adenylate cyclase, and is related to the reduction of AQP2 m-RNA synthesis (42), inhibition of adenosine triphosphatases, and interference with prostaglandin production (44). Lithium enters the collecting tubule cells via highly selective sodium and lithium channels, located in the apical membrane, causing increased sodium excretion and decreased renal tubule responsiveness to aldosterone and ADH. These channels are stimulated by aldosterone and inhibited by amiloride (45).

Up to 20% to 40% of patients chronically treated with lithium may develop NDI. Lithium use of the most common cause of acquired NDI (42,46), which is usually reversible after the withdrawal of the drug. However, in some cases it takes several months or years for the full re-establishment of the renal ability to concentrate urine (47). After prolonged use, even with discontinuation of the drug, some patients may have irreversible kidney damage due to a chronic interstitial nephropathy, with reports of evolution to end-stage renal failure (46), but the absolute risk seems to be small (0.5% compared with 0.2% in the general population) as shown by a recent review (18). In order to prevent renal toxicity, besides monitoring serum lithium and creatinin levels, a single daily dose of lithium should be preferred (46).

Thiazide diuretics are a therapeutic option in NDI, but hydrochlorothiazide has the potential to increase lithium toxicity, so it should be used with caution in these cases. Amiloride would be a better option because, besides its natriuretic action (causing contraction of extracellular volume, consequent decrease in glomerular filtration, and ultimately leading to decreased urine volume), it also reduces the entry of lithium in distal tubule cells (40). It is also important to be aware of the possibility of the coexistence of NDI and hypercalcemia related to lithium, since dehydration can exacerbate hypercalcemia. Another treatment option is a nonsteroidal antiinflammatory drug, such as indomethacin, but it should not be carried out on a long-term basis due to its side effects (46).

Hypothalamic-pituitary-adrenal axis

A study with patients in treatment for major depression showed that lithium led to an increased ACTH and cortisol response in the combined dexamethasone--CRH test, suggesting a possible effect of the drug on the hypothalamic-pituitary-adrenal axis (48).

In vitro studies demonstrate that lithium can inhibit apoptosis of human adrenal cortex, both in normal tissues and in tumors (49). On the other hand, lithium also inhibited the proliferation of pheochromocytoma cells by inhibiting the enzyme GSK3B (glycogen synthase kinase 3β), and promoting the suppression of chromogranin A, which represents a novel potential strategy for developing treatments of catecholaminergic tumors (50).

Glucose metabolism

Lithium has an inhibitory effect on amino acid- and glucose-induced insulin secretion by means of mechanisms related to microtubular function and calcium influx in pancreatic beta cells (51). Studies in rats showed that intravenous infusion of lithium leads to hyperglycemia, increased levels of glucagon and lower insulin response induced by both glucose and tolbutamide (52). These effects can be attributed to the action of catecholamines in the sympathetic-adrenal system, pro-

moting glycogenolysis, and to the direct effect of the drug on pancreatic alpha-2 and beta-adrenergic receptors, determining the reduction of insulin secretion and increased levels of glucagon (53).

On the other hand, lithium has also been associated with an insulin-like effect on glucose metabolism in skeletal muscle and adipocytes. In rat muscles, the drug increased the sensitivity of insulin-induced glucose transport, similar to the effects of exercise (54). Animal models also show that lithium promotes greater uptake of glucose by myocytes and glycogen synthesis, involving phosphorylation of AKT, GSK-3 inhibition, and increased p38-MAPK (mitogen-activated protein kinase) as mechanisms of action (55).

Effects on body weight

Weight gain up to 10 kg can occur in almost 30% of patients using lithium (44), by means of a mechanism that is still unclear, making therapy management more difficult (56). One possibility may be related to the stimulation of a greater intake of high-calorie beverages, especially in patients with polydipsia (44,57). Some studies also show changes in leptin levels, which ultimately can be involved in weight gain (58).

CONCLUSION

Considering all these aspects related to the use of lithium, it is important to be aware and familiar with all these potential endocrine disturbances when patients using this medication are followed up. Adequate monitoring is essential in order to identify possible complications and, thus, institute early and appropriate treatment.

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