LITHIUM USE AND PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Objective: To review suspected causes of lithium-induced hyperparathyroidism, disease presentation, underlying pathology, and current recommendations and trends in medical and surgical treatment.

Methods: Relevant literature was reviewed.

Results: Lithium carbonate therapy has continued to be a mainstay of treatment for bipolar disease and schizoaffective disorder since its introduction into clinical use. Several metabolic consequences are associated with its long-term use, including hypercalcemia and hyperparathyroidism.

Conclusions: Until further data become available, the surgeon should remain vigilant for the presence of pathologically active glands that may manifest their function at different times during the disease course. (Endocr Pract. 2011;17[Suppl 1]:31-35)

INTRODUCTION

Lithium carbonate therapy is an effective first-line treatment for a variety of psychiatric diseases and has been used since 1949 as a mood stabilizer (1). Effective use of the drug as a prophylactic treatment of recurrent mania and depression requires long-term maintenance therapy (2). Lithium therapy has also been shown to be effective in the management of acute manic episodes (2). Little is known about the mechanism by which it produces its stabilizing effect despite its widespread use and strong evidence of efficacy in these mood disorders (1,2). Although it is generally well tolerated, several endocrinopathies (nephrogenic diabetes insipidus, hypothyroidism, hyperthyroidism, hyperparathyroidism, and weight gain) are caused by or are associated with chronic lithium use (1-4). Hypercalcemia and hyperparathyroidism is an underappreciated, but relatively common occurrence, with a prevalence ranging from 6.3% to 50% in those patients requiring long-term lithium therapy (1). Numerous case reports published in the literature connect lithium therapy to hyperparathyroidism (5,6), yet lithium-induced hyperparathyroidism (LIH) continues to pose unanswered questions related to its etiology, as well as effective management.

BACKGROUND

A possible adverse effect of lithium carbonate therapy, namely hyperparathyroidism, was initially described in a case report in 1973 (4). Since then, several investigators have studied the effects of lithium on overall calcium metabolism (1,3,4). Lithium has a variety of known effects on calcium homeostasis with resultant biochemical findings noted on investigation. Serum calcium levels are elevated, although usually only slightly above the normal range (1,3,4). Intact parathyroid hormone (PTH) levels are typically mildly elevated, although in relationship to the increase in serum calcium, the PTH remains inappropriately normal or high-normal (3,4). The expected physiologic response to increasing calcium levels is to
decrease PTH secretion by negative inhibition. Therefore, one would expect low PTH levels in those patients with high or high-normal calcium levels. There is a decrease in urinary calcium excretion with resultant hypocalciuria, as well as typically normal serum phosphate levels (1). An increase in 1,25-dihydroxyvitamin D levels is thought to result from the normal physiologic actions of PTH on vitamin D metabolism as opposed to a direct effect of lithium on vitamin D metabolism (3).

ETIOLOGY

The mechanism by which lithium causes hyperparathyroidism is unclear. The parathyroid glands regulate calcium homeostasis through the actions of their hormone PTH. Lithium is thought to alter the set-point of calcium-triggered PTH secretion by direct actions on the parathyroid gland (1-4). It appears to antagonize the calcium-sensing receptor, thereby reducing the suppression of PTH by serum calcium (1,2). This increases the threshold of calcium needed to decrease PTH secretion, resulting in an abnormally elevated level of hormone at a given calcium concentration (1,3). Whether the lithium ion binds to the calcium-sensing receptor directly or affects its function through a different mechanism remains to be elucidated.

Another theory is one of direct stimulation of PTH secretion from the parathyroid cell itself. It is uncertain whether this is through direct stimulation of the normal cell or through potentiation of preexisting, albeit subclinical, parathyroid dysfunction. Lithium raises PTH levels through an increase in intact PTH released from parathyroid cells and not through changes in the renal excretion of the hormone or its metabolites (3). In in vitro studies, lithium stimulated PTH production in normal and hyperplastic cells, but not in adenomatous parathyroid tissue (2). Other studies have shown an apparent promotion of growth in preexisting abnormal tissue (2). These studies show an increase in DNA synthesis in abnormal human parathyroid cells when exposed to lithium, but this same increase was not seen in normal bovine parathyroids (2). To date, no studies have shown apparent gross chromosomal abnormalities in lithium-associated parathyroid tumors (2). As discussed in the following text, there appears to be an increase in multiglandular disease associated with LIH, but how lithium affects this change in disease presentation remains uncertain (7).

DIAGNOSIS

Regardless of the underlying mechanism, clinical studies have begun to explore the appropriate indications for treatment, as well as the approach to surgical therapy (5-11) (Fig. 1). First and foremost, the overall management begins by looking for and ruling out a preexisting disorder of calcium homeostasis before initiating lithium therapy (4). Not only does this practice address the potential of an underlying parathyroid disorder, but it also screens for metabolic disturbances that may worsen underlying psychiatric illness. In the absence of a preexisting condition, calcium levels should be closely monitored in the weeks following introduction of therapy. In rare instances, an acute rise in calcium is detected after lithium is started, which warrants rechecking calcium levels 2 to 6 weeks after initiating therapy (4). After initial close follow-up, yearly calcium levels are probably adequate for surveillance, although no prospective study is available for reference. Routine screening evaluation of PTH levels is not necessary until after abnormalities in calcium have been documented (4). As stated earlier, the biochemical abnormalities found in LIH are less pronounced than those seen in classic primary hyperparathyroidism, and the clinician must be aware of these potentially subtle changes in calcium homeostasis.

After documenting the biochemical presence of concurrent hypercalcemia and hyperparathyroidism, consideration must be given to the patient’s overall medical condition. Lithium and calcium ions correlate, and acute lithium toxicity should be ruled out initially (4). Evidence of symptomatic hypercalcemia should be elucidated, making note of worsening psychiatric illness, nephrolithiasis, osteoporosis, osteopenia, dehydration, renal impairment, and dyspepsia as common consequences of hypercalcemia. In the absence of a lithium overdose, the clinician must then decide between 3 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.

TREATMENT

When considering the first option, close cooperation with the treating psychiatrist is paramount in weighing the risks and benefits of transitioning to another psychiatric medication. Although there are other agents shown to be effective in acute mania, no other agent is as successful in prophylactic treatment of mood disorders (4). In fact, despite high initial response in transition therapy, the rate of relapse of manic symptoms is 28-fold higher in the first 3 months after discontinuation of lithium therapy (4). For these reasons, cessation of lithium therapy may not be feasible in some patients with LIH. In addition to the psychiatric consequences, there are still those patients who will remain hypercalcemic after cessation of lithium therapy, thus requiring further intervention (1,4). No definitive percentage of successful normalization of hypercalcemia after withdrawal has been documented, but normalization may take several weeks (1).

In the absence of clinical symptoms or severe hypercalcemia, it may be prudent to simply monitor calcium
levels, bone density, and kidney function while remaining on lithium therapy. No prospective study has been identified to speak to the frequency of monitoring, but it is generally accepted at an interval of 6 to 12 months as long as symptoms of hypercalcemia are absent (2,4). Evidence of increasing calcium levels, worsening bone density, poor control of psychiatric symptoms, or nephrolithiasis would prompt progression to a more aggressive treatment strategy. Another option has recently been reported in the literature for management of LIH. The calcimimetic class of drugs (cinacalcet) is an allosteric activator of the calcium-sensing receptor throughout the body (12). In parathyroid chief cells, this leads to lowering of the threshold of activation of the calcium-sensing receptor by extracellular calcium and a subsequent decrease in PTH secretion (12). To date, 5 patients have been described who have received cinacalcet with subsequent improvement in hypercalcemia during therapy (12,13). There have been no reported adverse effects, and the therapy was well tolerated (aside from financial expense) in each patient (12,13). Calcimimetics provide another potential therapy for patients with LIH considered poor operative candidates who cannot tolerate cessation of lithium or who remain persistently hypercalcemic after lithium withdrawal.

The indications for parathyroidectomy in both symptomatic and asymptomatic sporadic primary hyperparathyroidism have been well established. Despite this consensus, the indications for surgery in LIH are not as clear (1,2,10). It appears, however, that most clinicians make no distinction between the indications for operation for primary hyperparathyroidism and those for LIH. Consideration of surgical intervention is warranted in those patients with

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Fig. 1. Broad algorithm for the approach to lithium-induced hyperparathyroidism. PTH, parathyroid hormone.
hypercalcemia greater than 1 mg/dL above upper limit of the reference range, end-organ damage (osteoporosis, nephrolithiasis), or worsening neurocognitive symptoms.

**SURGICAL THERAPY**

The approach to the surgical management of primary hyperparathyroidism has undergone a fundamental shift since the introduction of PTH monitoring and the validation of minimally invasive parathyroid exploration. Debate remains, however, as to the appropriate surgical approach in LIH. Given the lack of concrete information regarding the etiology of LIH, decisions on surgical management have so far been based on small case series, individual experience, and retrospective reviews (5-11). Although no absolute recommendations can be set forth now, the data do draw attention to several pitfalls and divergences when approaching the patient with LIH as opposed to the patient with sporadic primary hyperparathyroidism.

The primary debate concerns the rates of multiglandular disease encountered in LIH and its subsequent effect on the results of surgical therapy. Since LIH was first brought to the surgical literature by McHenry et al in 1990, the pathologic findings have been reviewed by several authors (5-11). Overall rates of multiglandular disease have ranged from 25% to 75% (Table 1) (5, 7-11). Regardless of the actual rate of multiglandular disease, the data strongly suggest a significantly higher rate of multiglandular disease in patients exposed to lithium compared with those with sporadic primary hyperparathyroidism. This is probably because lithium, as it circulates systemically through the body, exerts its expected effect on all 4 parathyroid glands. In fact, it appears strange that there is still such a high rate of single adenomas as the cause of LIH. Pending more data concerning the actions of lithium on parathyroid tissue, the true pathology of this disease remains debatable. As an example, a recent case report documents a patient, apparently cured after single-gland parathyroidectomy, who presented with recurrent hyperparathyroidism and multiglandular findings 5 years later (6). Whether this case represents missed multiglandular disease at initial operation or the ongoing differential effects of lithium on parathyroid function remains unclear. Until the impact of lithium on parathyroid function can be elucidated, the surgeon is left to approach each case with caution. A high degree of suspicion must be maintained to detect the presence of other diseased glands and has led to the recommendation by several authors for routine bilateral neck exploration in patients with LIH (6,7,9).

There are groups that advocate the use of directed parathyroidectomies in patients with LIH (8,10). Awad et al reviewed their experience in 15 patients with LIH and addressed the need for subtotal resection. Of those 15 patients, 14 were found to have adenomas on pathologic examination and only 1 presented with parathyroid hyperplasia. However, 3 of the patients with adenomas did have double adenomas rather than single-gland disease. When including these 3 patients, the rate of multiglandular disease was 27% (4/15). Importantly, each patient underwent routine bilateral neck exploration, visualization of all glands, and removal of only the enlarged ones, without the use of intraoperative PTH monitoring (11). The authors concluded that adenomatous transformation of the parathyroids, rather than diffuse hyperplasia, is the dominant pathologic finding in LIH. On the basis of this observation, they further recommended excision of only visually abnormal disease rather than routine 3.5-gland parathyroidectomy (11). This approach differs from the current limited/minimally invasive approaches to primary sporadic hyperparathyroidism that rely heavily on preoperative localization studies and intraoperative PTH monitoring to avoid missing multiglandular disease when other glands are not routinely visualized.

Carchman et al reviewed their experience in 16 patients with LIH and report the rate of multiglandular disease to be 25%. In their control group of 1191 patients with sporadic

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Abbreviation: NA, not applicable.
primary hyperparathyroidism over the same study period, only 146 (12.3%) demonstrated multiglandular disease. Although apparently divergent, the change did not meet significance on evaluation with the Fisher 2-tailed test ($P = .13$). With a calculated power of 0.25, a very possible type II error may exist, meaning a larger series may indeed show a significant difference in the rate of multiglandular disease. Routine technetium Tc 99m sestamibi single-photon emission computed tomography was performed in all patients. In those without localizing or bilateral findings on imaging, the right side was arbitrarily explored first. All patients had an attempt at unilateral exploration guided by intraoperative PTH monitoring, although 8 of 16 required bilateral exploration on the basis of intraoperative findings. In the 12 patients with pathologically confirmed single-gland disease, the authors were able to perform a successful unilateral exploration in 8 (67%). All patients were normocalcemic at a mean follow-up of 16 months (range, 5-50 months). They concluded that intraoperative PTH monitoring–guided parathyroidectomy is an appropriate therapy in LIH, with bilateral exploration reserved for those patients who do not meet their established intraoperative PTH criteria (50% decrease from baseline with final PTH value within the normal range) (10).

At this time, on the basis of the available scientific evidence, no conclusive decision can be reached as to the best operative approach to LIH. Three main surgical approaches remain available to the surgeon: (a) unilateral/focused parathyroidectomy guided by preoperative localization and intraoperative PTH monitoring with bilateral exploration in those who do not meet curative criteria, (b) routine bilateral neck exploration with removal of only those visually abnormal glands with or without preoperative localization or intraoperative PTH monitoring, or (c) bilateral neck exploration with subtotal (3.5 gland) parathyroidectomy in all patients. The authors favor an attempt at unilateral/focused parathyroidectomy. All patients undergo routine, preoperative, surgeon-performed ultrasonography followed by sestamibi scanning. In those patients with indications of single-gland disease, intraoperative PTH monitoring–guided parathyroidectomy is performed. Those patients who do not meet established intraoperative PTH monitoring criteria undergo conversion to bilateral exploration with visualization of all glands.

**CONCLUSION**

The currently available data support a higher rate of multiglandular disease, which remains teleologically sensible given the chronic systemic exposure to lithium. No long-term study exists to document the durability of success from minimally invasive techniques to treat LIH. At this time, further basic science research concerning the etiology of LIH must be conducted to fully understand the disease process. There is agreement, however, that those patients with hypercalcemia, hyperparathyroidism, and the accepted indications for parathyroidectomy do benefit from surgical exploration. Until further data become available, the surgeon should remain vigilant for the presence of pathologically active glands that may manifest their function at different times during the course of the disease. A direct/limited approach may be appropriate, so long as criteria are strictly adhered to and the limitations of the technique are appreciated in this select population of patients with LIH. Prophylactic 3.5-gland parathyroidectomy does not appear to be warranted given the available data. For those individuals in whom surgery is deemed inappropriate or too risky, therapy with calcimimetics may provide an alternative to classic glandular excisions.

**DISCLOSURE**

The authors have no multiplicity to disclose.

**REFERENCES**