Management of lithium-associated hyperparathyroidism with cinacalcet hydrochloride

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Introduction

Lithium-associated hyperparathyroidism is an under-recognised side effect of chronic lithium therapy. This ill-defined endocrinopathy consists of various biochemical abnormalities, including overt hyperparathyroidism, hypercalcaemia with inappropriately normal parathyroid hormone level and normocalcaemia with raised parathyroid hormone levels. There is a lack of clear guidance regarding the management of lithium-associated hyperparathyroidism. This article reports the case of a 54-year-old woman with lithium-associated hyperparathyroidism who was successfully managed with cinacalcet, without discontinuing lithium therapy. Cinacalcet may provide an alternative to surgery, especially in patients with mild disease, and in those who either refuse or have contraindications to surgery.

Discussion

Lithium-associated hyperparathyroidism is biochemically characterised by an elevated or inappropriately normal parathyroid hormone level with hypercalcaemia in patients taking lithium. Additional findings in lithium-associated hyperparathyroidism include hypermagnesaemia, normophosphataemia and hypocalciuria (in the initial setting) (Mifsud et al, 2020).

Case report

A 54-year-old postmenopausal woman with a long history of bipolar affective disorder treated with lithium was being followed up at the endocrine outpatients for probable lithium-associated hyperparathyroidism. Over the previous 11 months, the patient had developed gradually worsening hypercalcaemia, with her latest calcium level being 3.06 mmol/litre.

The patient was asymptomatic and physical examination was unremarkable. Laboratory investigations revealed moderate hypercalcaemia (corrected calcium 3.06 mmol/litre), hypophosphataemia (0.70 mmol/litre) and hypermagnesaemia (1.31 mmol/litre). Serum creatinine level and liver function tests were within normal limits. Subsequent investigations revealed an inappropriately elevated parathyroid hormone level of 255 pg/ml (normal range 15–65 pg/ml) and vitamin D deficiency (serum 25-hydroxyvitamin D 25 ng/ml; normal range 30–100 ng/ml). The calcium:creatinine clearance ratio was 0.03. A dual-energy X-ray absorptiometry (DEXA) scan revealed a femoral neck T-score of -2.0 and a total lumbar spine T-score of -1.3, suggestive of osteopenia.

Pre-operative localisation scans for lithium-associated hyperparathyroidism included ultrasound of the neck and technetium-99m sestamibi parathyroid scintigraphy, neither of which revealed evidence suggestive of a parathyroid adenoma.

Treatment options discussed with the patient included discontinuation of lithium (following discussion with the patient's psychiatrist) with vigilant surveillance of her calcium levels or referral for surgery with cinacalcet initiation in the interim. The option of discontinuing lithium was immediately rejected by the patient as she feared that this would exacerbate her underlying psychiatric condition, as had happened previously when lithium was switched to other mood stabilisers. A review of her previous medical records and a discussion with her psychiatrist confirmed this.

Therefore, the patient was started on cinacalcet 30 mg twice daily and referred for a consultation with the endocrine surgeons for consideration of bilateral neck exploration and parathyroidectomy. The patient was seen by the endocrine surgeons and she refused surgery. She was followed up as an outpatient with regular monitoring of her serum calcium levels. She is currently normocalcaemic on cinacalcet 60 mg twice daily (latest calcium level 2.40 mmol/litre).

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Lithium has an inhibitory effect on the calcium-sensing receptor, which increases the set point at which the parathyroid cells stop secreting parathyroid hormone. Inhibition of the calcium-sensing receptor also leads to increased reabsorption of calcium in the renal tubules, independent of parathyroid hormone and serum calcium levels, leading to hypercalcaemia and hypocalciuria (Szalat et al, 2009). Apart from these acute effects of lithium on the parathyroid chief cells and thick ascending limb of the loop of Henle, chronic lithium use may also lead to increased parathyroid mass as a result of hyperplastic or adenomatous change (Mallette et al, 1989; Nordenström et al, 1992). Hence, long-term lithium therapy may cause chronic effects that are identical to those of primary hyperparathyroidism, which become independent of the presence or absence of lithium. These effects can cause serious end-organ damage, similar to those seen in primary hyperparathyroidism (Naramala et al, 2019).

There is a lack of guidance on the management of lithium-associated hyperparathyroidism. Since demographic trends of lithium-associated hyperparathyroidism are similar to those seen in primary hyperparathyroidism, guidelines for treating primary hyperparathyroidism can provide a framework for the management of lithium-associated hyperparathyroidism (Shapiro and Davis, 2015). Patients who are symptomatic or fulfil any of the criteria of the 2014 international guidelines for the management of asymptomatic primary hyperparathyroidism should be referred for surgery (Bilezikian et al, 2014). Asymptomatic patients, or those considered high risk for surgery, as well as patients who do not fulfil the criteria for surgical resection, should ideally have lithium discontinued after a multidisciplinary discussion with the patient and their psychiatrist. These patients need careful surveillance of their calcium levels and can also be considered for calcimimetic therapy with cinacalcet (Sloand and Shelly, 2006; Marcocci and Cetani, 2012).

This case supports other reports of cinacalcet being used to successfully manage lithium-associated hyperparathyroidism. Cinacalcet initiation allowed the patient to continue taking lithium for her bipolar affective disorder while restoring normocalcaemia (Dixon et al, 2018).

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Learning points

- Lithium can cause various endocrinopathies and metabolic disturbances, including hypercalcaemia, thyroid dysfunction and nephrogenic diabetes insipidus.
- Lithium may cause hypercalcaemia through both acute and chronic effects. Acute and initial effects of lithium on the calcium-sensing receptor pathway may be reversed. Long-term lithium treatment can cause irreversible changes in the parathyroid glands and can lead to hyperparathyroidism.
- Regular monitoring of calcium levels in patients treated with lithium is vital since lithium-associated hyperparathyroidism is associated with increased morbidity, and early diagnosis and timely management are associated with improved outcomes.
- Patients with lithium-induced hyperparathyroidism should be managed within a multidisciplinary team, which ideally includes an endocrinologist, a psychiatrist and a surgeon, to improve the patient's quality of life.

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