

Potentialiation of Endocrine Adverse Effects of Lithium by Enalapril and Verapamil

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ABSTRACT

Lithium, which is widely used in the management of patients with bipolar disorder, may alter the function of some endocrine organs, particularly the thyroid and parathyroid glands, as well as it may reduce the sensitivity of the kidneys to vasopressin. In most lithium-treated patients, endocrine abnormalities are limited to one endocrine organ and are observed only after long-term lithium therapy. The patient reported in this study developed hypothyroidism, hyperparathyroidism and nephrogenic diabetes insipidus. However, the last two disorders were induced by a small increase in plasma lithium levels as a result of the treatment with enalapril and verapamil. This case shows that patients at high risk of thyroid, parathyroid or renal disorders receiving lithium should not be treated with drugs known to interfere with plasma lithium levels.

Keywords: Hypothyroidism, hyperparathyroidism, lithium, nephrogenic diabetes insipidus

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RESUMEN

El litio, ampliamente utilizado en el tratamiento de pacientes con trastorno bipolar, puede alterar la función de algunos órganos endocrinos, particularmente la tiroides y las glándulas paratiroides, así como reducir la sensibilidad de los riñones a la vasopresina. En la mayoría de los pacientes tratados con litio, las anomalías endocrinas se limitan a un órgano endocrino, y se observan solamente después de la terapia con litio a largo plazo. El paciente reportado en el presente estudio, desarrolló hipotiroidismo, hiperparatiroidismo, y diabetes insípida nefrógica. Sin embargo, los dos últimos trastornos fueron inducidos por un pequeño aumento en los niveles del litio en plasma, como resultado del tratamiento con enalapril y verapamilo. Este caso demuestra que los pacientes que reciben litio, y presentan alto riesgo de trastornos de la tiroides, paratiroides o renales, no deben ser tratados con medicamentos de los cuales se sabe que interfieren en los niveles de litio plasmático.

Palabras claves: Hipotiroidismo, hiperparatiroidismo, litio, diabetes insípida nefrogénica

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INTRODUCTION

Lithium salts, drugs commonly used in the management of bipolar disease, are characterized by a narrow therapeutic index, with therapeutic levels between 0.6 and 1.5 mEq/L (1, 2). Patients receiving lithium salts often require to be treated with these agents on a chronic basis. Unfortunately, long-term lithium treatment is relatively frequently associated

with the risk of the development of adverse effects, particularly gastrointestinal effects (nausea, vomiting, diarrhoea, abdominal pains), neurological effects (tremor, dysarthria, lethargy, nystagmus, ataxia) and different endocrine complications (3, 4). Although lithium salts may induce hypothyroidism, hyperparathyroidism and nephrogenic diabetes insipidus in most patients, endocrine complications are limited to only one endocrine organ, mainly the thyroid gland (4–7). The risk of adverse effects is higher if plasma lithium levels exceed therapeutic levels (3, 4) and therefore some agents, including angiotensin-converting enzyme inhibitors and calcium channel blockers, which increase plasma lithium levels (8, 9), may potentiate its toxicity theoretically.

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In this paper, we present a case of a man with hypothyroidism induced by chronic treatment with lithium carbonate. Shortly after the introduction of therapy with an angiotensin-converting enzyme inhibitor and a non-dihydropyridine calcium channel blocker, the patient developed primary hyperparathyroidism and nephrogenic diabetes insipidus.

CASE REPORT

The patient, presently 65 years old, started lithium carbonate treatment 24 years ago because of bipolar disorder. The drug, administered at the daily dose of 900 mg, was found effective in relieving the symptoms of this disorder and for the first eight years produced no serious adverse effects. The patient claimed to have complied during this period of time with the prescribed treatment. Unfortunately, although plasma lithium levels were then occasionally measured, the patient did not have the results of these measurements. After eight years of lithium treatment, the patient developed hypothyroidism (thyroid-stimulating hormone (TSH) – 11.2 mIU/L, reference values: 0.4–4.5 mIU/L; free thyroxine – 8.8 pmol/L; reference values: 9.0–22.0 pmol/L) and therefore was prescribed with levothyroxine at the initial daily dose of 50 µg. After two months of levothyroxine replacement, the patient became euthyroid (TSH – 0.95 mIU/L) and therefore lithium carbonate treatment could be continued. At that time, neither the size of the gland nor thyroid antibodies were investigated. For the following 10 years, thyroid function gradually declined and levothyroxine dose had to be titrated up to 100 µg daily. During all this time, plasma lithium levels were within the reference range (0.9–1.1 mEq/L).

Six years ago, the patient was admitted to our clinic in order to establish the cause of hypertension. Despite normal levels of TSH (1.35 mIU/L), free thyroxine (15.9 pmol/L) and free triiodothyronine (2.9 pmol/L), the titre of thyroid peroxidase antibodies was high (985 IU/mL; reference values below 100 IU/mL), and ultrasonography of the thyroid gland revealed moderate hypoechogenicity. A magnetic resonance imaging of the neck, performed because of suspected enlargement of cervical lymph nodes, showed normal structure of the thyroid and adjacent structures. Because no secondary cause of hypertension was found, the patient was prescribed with enalapril and verapamil at the daily doses of 20 mg and 240 mg, respectively. Although this treatment normalized blood pressure, six months later, the patient started to experience nausea, vomiting and constipation, and after the following two months, developed acute pancreatitis, due to which he was hospitalized.

Laboratory investigations carried out a week later revealed hypercalcaemia (plasma calcium levels corrected for albumin – 2.82 mmol/L, reference values: 2.20–2.60 mmol/L; ionized calcium – 1.5 mmol/L, reference values: 0.9–1.3 mmol/L), which was accompanied by increased plasma magnesium levels (1.5 mmol/L; reference values: 0.8–1.3 mmol/L), normophosphataemia (1.3 mmol/L;

reference values: 0.9–1.5 mmol/L), normal 25-hydroxyvitamin D plasma levels (43 ng/mL; reference values: 30–75 ng/mL) and hypocalciuria (2.2 mmol/day; reference values: 3.0–7.5 mmol/day). The patient also started to experience some symptoms of hypothyroidism (fatigue, cold intolerance, muscle cramps and weight gain), which were accompanied by an increase in plasma TSH levels (7.25 mIU/L) and therefore the daily dose of levothyroxine had to be increased to 175 µg. The presence of primary hyperparathyroidism was supported by the finding of elevated plasma intact parathyroid hormone (PTH) assessed using an immunoradiometric assay (148 ng/L; reference values: 15–75 ng/L) and retention of the isotope at the upper pole of the right thyroid lobe.

Plasma lithium levels (1.30 mEq/L) were higher than previously, but did not exceed the upper limit of the reference range. The patient was diagnosed with primary hyperparathyroidism and underwent parathyroidectomy, which resulted in a normalization of parathyroid function. Although his clinical condition markedly improved, eight months later, he started to complain of polydipsia and polyuria with pronounced nocturia. A magnetic resonance imaging scan of the patient's brain revealed no abnormalities in the sella turcica. The in-and-out balance of fluids was nine litres given and seven litres excreted. The urinalysis was normal except for the low specific gravity (1.004). Serum and urine osmolality were 302 and 120 mOsm/kg H₂O, respectively. Serum arginine vasopressin level was 108 pg/mL (normal 4–12 pg/mL).

An overnight water deprivation test, lasting 14 hours, was stopped because three consecutive samples differed by less than 30 mOsm/kg and because of weight loss of 4%. At the end of this test, urine osmolality reached the value of 210 mOsm/kg, with a failure to increase after desmopressin injection. Because both clinical symptoms and laboratory findings suggested nephrogenic diabetes insipidus, the patient started the treatment with indomethacin and amiloride, which resulted in only partial improvement (diurnal fluid intake – 5 L, diurnal diuresis – 4 L). Although during the whole therapy with enalapril and verapamil, plasma lithium levels were within therapeutic limits (1.3–1.5 mEq/L), we decided to stop further administration of these agents. After 10 days, fluid intake and diuresis normalized, plasma lithium levels lowered to 1.0 mEq/L and, because of clinical improvement, the dose of levothyroxine could be reduced.

Presently, four years after enalapril plus verapamil treatment termination, the patient feels well. Plasma lithium levels are in the range of 0.8–1.1 mEq/L. Calcium-phosphate homeostasis and water-electrolyte balance are undisturbed (plasma calcium levels corrected for albumin – 2.45 mmol/L, phosphates – 1.2 mmol/L, diurnal diuresis – 1.4–1.8 L). Although hypothyroidism and thyroid autoimmunity are still present, the dose of levothyroxine required to maintain

plasma TSH within the normal range (100 µg) is lower than during the therapy with enalapril and verapamil.

DISCUSSION

Although thyroid dysfunction, abnormally high plasma calcium levels and nephrogenic diabetes insipidus are the most frequent endocrine complications associated with chronic lithium treatment (4–7), to the best of our knowledge, only one previous report described that lithium may induce the development of all these complications in the same patient (10). Although hypothyroidism, particularly its subclinical form, is commonly observed in the general population, it seems that in the index patient, hypothyroidism, at least in part, was secondary to lithium therapy.

Hypothyroidism appeared several years after the introduction of lithium treatment, the dose of levothyroxine required to maintain thyroid function within normal limits increased with time, the patient had no family history of thyroid disorders, and the requirements for thyroid hormones markedly increased in the period during which the patient additionally received enalapril and verapamil – the drugs devoid of any significant effect on thyroid function – and decreased shortly thereafter. This hypothyroidism was probably secondary to a multi-directional effect of lithium on the thyroid gland.

Lithium was found to inhibit iodine uptake, change thyroglobulin structure (by interfering with the coupling of iodotyrosine residues to form iodothyronines), inhibit thyroid hormone release, reduce deiodination of thyroxine to triiodothyronine, increase nuclear triiodothyronine binding, and to induce thyroid autoimmunity by enhancing lymphocyte secretion of immunoglobulins (11). However, the most interesting finding of our study was that, with the exception of hypothyroidism, all the remaining endocrine abnormalities developed in a relatively short period of time after the onset of enalapril and verapamil treatment, although lithium had already been administered to the patient for several years. Because both angiotensin-converting enzymes inhibitors and calcium channel blockers were found to increase circulating lithium concentrations (8, 9), they probably induced hyperparathyroidism and diabetes insipidus by increasing lithium concentration and, consequently, lithium toxicity.

Lithium treatment seems to cause hyperparathyroidism in two different ways. By interfering with the calcium sensing receptor, it decreases the affinity of this receptor to calcium ions and, consequently, it alters the set point for PTH secretion. Alternatively, it may stimulate the growth of pre-existing parathyroid tumours, causing an earlier clinical manifestation of PTH excess (7). Interestingly, in the index patient just before the onset of enalapril and verapamil treatment, no abnormalities in both calcium-phosphate homeostasis and magnetic resonance imaging of the neck were observed. The fact that our patient developed a parathyroid adenoma within only a few months suggests that in

selected individuals, hyperparathyroidism may be associated with rapid enlargement of the parathyroid glands initially free from any pathology, or containing only a tumour or tumours of microscopic size.

The association of hyperparathyroidism with lithium treatment is also supported by finding normal phosphate content, increased circulating magnesium and hypocalciuria in the index subject. [In most patients with hyperparathyroidism, plasma phosphates and urine calcium loss are increased (12).] These findings may be attributed to the inhibitory effect of lithium on phosphate excretion and activity of the renal calcium sensing receptor. Because of acute pancreatitis, the patient was subjected to surgical removal of the enlarged gland. In light of the recent results, an alternative option may be the use of calcimimetics, which, stimulating the calcium sensing receptor, produce the opposite effect to lithium (13).

Interestingly, only enalapril and verapamil withdrawal resulted in a normalization of the water-sodium balance. Some effect on the urine volume was, however, exhibited by the treatment with amiloride/indomethacin combination. This effect may be attributed to the inhibitory effect of amiloride on the entrance of lithium into the cells of the distal tubule as well as to the indomethacin-induced increase in cyclic adenosine monophosphate (secondary to a reduction in phosphodiesterase activity) and to the indomethacin-induced stimulation of the sodium reabsorption in the medullary thick ascending loop of Henle (7). Paradoxically, indomethacin was effective, although non-steroid anti-inflammatory agents may increase the toxicity of lithium salts (14). It should be mentioned that although enalapril and verapamil increased plasma lithium levels, these levels never exceeded the upper limit of normal. This means that in predisposed patients, endocrine abnormalities may develop even if lithium levels are within the reference range.

In conclusion, our study has shown that chronic lithium treatment may result in the development of complications in several endocrine organs in the same patient. The risk is particularly high if the patient is concomitantly treated with drugs interfering with circulating lithium levels; therefore the administration of these agents should be avoided in lithium-treated patients having endocrine abnormalities already at baseline conditions.

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