

Case Study

NON PITTING TYPE PEDAL EDEMA WITH LITHIUM: A CASE REPORT

PARVATHYPRIYA C., JESLYN MARY PHILIP, CHRISTEENA GEORGE, LAKSHMI R.

Department of Pharmacy Practice, Amrita School of Pharmacy, Kochi, Amrita Vishwa Vidyapeetham, Amrita University, India
Email: lakshmir@aims.amrita.edu

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ABSTRACT

Objective: To report a case of lithium induced bilateral nonpitting pedal edema.

Methods: The clinical data of a bipolar affective disorder patient with current episode of mania and psychotic symptoms who experienced bilateral non pitting pedal edema with lithium.

Results: The patient was a 29 yr old female who developed bilateral non-pitting type pedal edema with lithium therapy with normal plasma lithium level (0.72mEq/l). She is a known case of bipolar affective disorder (BPAD) was admitted to psychiatry department with episode of mania with psychotic symptoms. She had history of drug induced hypersensitivity reaction with eosinophilia and systemic symptoms (DRESS) with oxcarbazepine and so the drug was discontinued and was started on tablet lithium 400 mg twice daily. On admission here, the dose of lithium was increased to 1200 mg/day. The patient gradually improved but she developed bilateral non-pitting pedal edema. Serum lithium concentration was normal and there were no other early symptoms of lithium toxicity. But as the patient's distress further increased with increasing pedal edema, it was decided to stop lithium altogether and to maintain the patient on tablet quetiapine 800 mg therapy for BPAD. Within one week of stopping lithium the edema on both her feet decreased significantly. Causality was assessed by naranjo causality assessment scale and a probable relationship was obtained between lithium and pedal edema with a score of 6.

Conclusion: This case emphasises that regular physical examination and laboratory investigations are important for patients who are on lithium therapy. Clinicians should always be careful while initiating lithium treatment in a patient with respect to the initial dose and dose escalation even after a period of successful therapy with lithium, as minor dose escalation can cause major changes in the serum lithium concentration and thereby the patient's tolerability to lithium.

Keywords: Pedal edema, Lithium, Mania

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INTRODUCTION

Lithium is widely used to treat and prevent episodes of mania in bipolar disorder. It is a mood stabiliser. It is also used for the treatment of aggression, post-traumatic stress disorder, and conduct disorder in children and as an augmenting agent for antidepressants [1]. It is available as both immediate and extended release formulations. For treatment of acute mania, it is initiated at low doses of 300 mg three times daily or less, gradually increasing based on response and tolerability of patients. The daily dose can go up to 1800 mg in 3 to 4 divided doses.

Lithium's mechanism of action is not well understood. It mainly affects two intracellular signalling pathways namely inositol monophosphate and glycogen synthase kinase pathway. Through the action in inositol monophosphate pathway, it reduces intracellular inositol which can be the mechanism behind mood stabilising effect of lithium. By inhibition of glycogen kinase-3, it influences energy metabolism, neuroprotection and neuroplasticity [2].

In addition to its therapeutic role, it is important to monitor patients closely, to prevent occurrence of side effects as lithium has got a narrow therapeutic index. A large proportion of patients experienced at least one episode of toxicity during chronic lithium therapy [3]. Most common side effects of chronic lithium therapy is hand tremors, polydipsia, polyuria, weight gain, diarrhoea and edema in face and legs [4]. Lithium can also cause various serious side effects like cardiac arrhythmias, circulatory shock, blackout spells, headache, psychomotor retardation, acne vulgaris, and exacerbation of psoriasis, hypothyroidism, diabetes insipidus, anorexia, gastritis, oliguria, leukocytosis and tremors [7].

Cases with lithium-induced pedal edema are significant as it can even occur in normal serum lithium concentration. Here we are discussing a case of lithium-induced bilateral pedal edema in a

patient who has no hepatic renal or cardiovascular disease. Mechanism of this phenomenon is not well understood as laboratory investigations were all normal. Demers *et al.* postulates that edema can be due to a marked increase in sodium intake which may be induced in part by mania or reduction in sodium excretory capacity induced by lithium [5].

CASE REPORT

A 29 y old female, k/c/o BPAD came with complaints of fever with rash for 2 d with a preceding history of starting new psychiatric medications 15 d prior to the episode. She was on tablet oxcarbazepine 900 mg, tablet quetiapine 600 mg, tablet zolpidem 10 mg and tablet clonazepam 1 mg, all for daily dosing. These medications were prescribed for a mood disorder, insomnia and to control psychotic symptoms associated with mania. On examination, she was found to have facial puffiness with rashes over the face and back. Initial lab investigations showed elevated SGOT of 41.8 IU/l (5-35 IU/l), SGPT of 74.2 IU/l (5-45 IU/l), with absolute eosinophilia of 26.3% (1-8%). She was admitted with a provisional diagnosis of oxcarbazepine induced hypersensitivity reaction. For this she was started on symptomatic management with methylprednisolone, antihistamine and antipyretics and continued on her psychiatric medications except for oxcarbazepine which was suspected as the cause of her drug-induced hypersensitivity reaction. Dermatology consultation was sought and the same line of management was optioned. Psychiatry consultation was sought and doses of quetiapine and zolpidem were increased and also added tablet lithium 800 mg daily for management of mania. Her facial puffiness decreased markedly and her rashes decreased and she got discharged in a stable condition with the above-mentioned management.

After one week she got admitted at the department of psychiatry due to an episode of mania with psychotic symptoms. She was continued on 20 mg of zolpidem and 700 mg quetiapine for insomnia and

psychotic symptoms. Doses of methylprednisolone were gradually tapered as indicated. On this admission, the dose of lithium was increased to 1200 mg daily for effective management of mania. Meanwhile, the patient developed bilateral non-pitting pedal edema. It was initially expected that with the tapering of methylprednisolone edema would disappear, but rather it increased.

The patient was thoroughly investigated. All laboratory parameters were within normal limits. Serum lithium estimation was done and the concentration was 0.72mEq/l which was normal (0.5-1.2 mEq/l). Dermatology consultation was done and their advice for symptomatic relief was carried out. Medicine consultation was sought and they advised to start on tablet lasix 40 mg, but it was not given as furosemide increases serum lithium concentrations. Repeat laboratory investigations and clinical examinations were done and she was found to have oliguria and leukocytosis (18k/uL), both being reported side effects of lithium in literature. Lower limb doppler was done to rule out deep vein thrombosis.

With time patient's distress due to edema increased and it was decided to withhold lithium as lithium-induced edema was also kept in mind in spite of its normal serum concentration. Following this edema subsided gradually and the patient received increased dose of tablet quetiapine (800 mg) for the management of manic symptoms. After ten days edema disappeared completely from both of her lower limbs, but she started developing increased talk and irritability. So it was decided to restart lithium at a low dose of 400 mg daily, and she was tolerating this dose well without other side effects. It was augmented with sodium valproate. Family members were educated regarding the nature of her illness. Her manic symptoms improved well with this treatment, with no other side effects and she was discharged in a stable condition.

DISCUSSION

Lithium is a mood stabilizer which is used in the management of mania associated with bipolar disorder [7]. Chronic lithium therapy is always associated with one or more episodes of its side effects [3]. It is important to regularly monitor patients for side effects while they are on lithium as it's a drug having a narrow therapeutic index (0.5-1.2mEq/l) [6]. Only a few reported cases of lithium-induced pedal edema is there. In this case report, side effect occurred at a normal serum lithium concentration which shows regular clinical assessment of patients is more important than laboratory investigations. Mild adverse reactions can occur even if serum lithium level is 1 mmol/l. At a level of 1.5 to 2 mmol/l moderate toxicity occurs and above which severe toxicity occurs [7].

Tushar *et al.* described a similar case of bilateral pitting pedal edema with lithium therapy where furosemide was not given to resolve edema, rather they stopped lithium as similar to this case. Lithium's main side effect in the kidney is nephrogenic diabetes insipidus which occur as a result of an inability to concentrate urine by the nephrons due to the lithium-induced insensitivity of tubular cells towards antidiuretic hormone. Postulated treatment for this condition is with thiazide diuretics [7]. Vestergaard *et al.* studied clinically significant side effects of lithium in 237 patients and found that edema in face or legs induced by lithium were only seen in one

tenth of the patients [4]. Demers *et al.* report nine consecutive cases of pretibial edema in patients who have been taking lithium carbonate where the edema resolves with spironolactone, that indicates a positive relation between tubular reabsorption of sodium and edema [5]. But in this case, edema was due to patient's intolerance to high dose lithium (1200 mg/day). So when lithium therapy was withheld, the patient improved significantly.

Later it was found that patient is tolerating low doses of lithium. This case report emphasises on the significance of narrow therapeutic index of lithium as here dose elevation (1200 mg) is the cause of adverse drug reaction which was not seen in the lower doses (800 mg) that the patient was taking prior to admission. Re-challenging the patient with a lower dose of lithium showed that she was tolerating it well (400 mg). Causality was assessed by naranjo causality assessment scale and a probable relationship was obtained between lithium and pedal edema with a score of 6.

CONCLUSION

This case emphasises that regular physical examination and laboratory investigations are important for patients who are on lithium therapy. Clinicians should always be careful while initiating lithium treatment in a patient with respect to the initial dose and dose escalation, even after a period of successful therapy with lithium, as minor dose escalation can cause major changes in the serum lithium concentration and thereby the patient's tolerability to lithium.

CONFLICTS OF INTERESTS

Declared none

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