Clinical Case Report

Lithium-induced sinus node dysfunction at therapeutic serum levels

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ABSTRACT

Lithium-induced cardiotoxicity, though rare at therapeutic levels, has been reported frequently in overdoses. We report a patient who developed sinus bradycardia while being treated with lithium carbonate even though the serum lithium levels were within the therapeutic range. It reversed following withdrawal of lithium and did not reappear with subsequent treatment with valproate.

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INTRODUCTION

Lithium is the preferred option for the treatment of manic episodes. A serum level of 0.8–1.2 mEq/L is required and can be achieved with a dose of 900–1200 mg/day.[1] The cardiac side-effects of lithium are well described at both therapeutic and toxic serum levels.[2] Asymptomatic electrocardiogram (ECG) changes are the most common (10%–30%) including T wave changes such as flattening, isoelectricity or inversion.[3] Infrequently, clinically evident cardiac manifestations occur including sinus node dysfunction,[4] and rarely, prolonged QT interval, atrial flutter, atrioventricular block, right bundle branch block, left anterior hemiblock, ventricular tachycardia and ventricular fibrillation.[5] Very rarely, ventricular tachycardia and ventricular fibrillation resulting in death have also been reported.[2] Rarely, profound bradycardia has been reported to occur with chronic lithium poisoning, even when serum lithium concentrations appear to be declining.[6] We report a patient with lithium-induced bradycardia while the serum lithium level was within the therapeutic range.

THE CASE

A 30-year-old unmarried man belonging to the low socioeconomic stratum was admitted to our hospital with an episode of mania for 3 weeks. He had 4 previous episodes of mania requiring admission to hospital. In the last episode, he was prescribed lithium carbonate 900 mg/day along with olanzapine 10 mg/day. His baseline investigations including haemogram, renal and liver function tests, serum electrolytes and ECG were normal. He responded well and had serum lithium levels within the therapeutic range (0.94 mmol/L and 1.06 mmol/L on two occasions), without any emergent adverse effects. The present episode occurred following discontinuation of medications for 2 months. On the day of admission, his blood pressure was 110/80 mmHg and his pulse rate was 80/minute with a regular rhythm. The haematological, renal and liver function tests, serum electrolytes and ECG were normal. He was started on lithium carbonate 900 mg/day and olanzapine 10 mg/day, considering his past response to lithium. His serum lithium level was 0.81 mmol/L after 5 days of treatment and 0.94 mmol/L after 1 week. Over the next 2 weeks his manic symptoms improved. During the third week, his pulse rate decreased to 44/minute but was regular, though he had no symptoms. An ECG done on the same day showed a heart rate of 39/minute without any other abnormalities. There was no history of exposure to any other cardiotoxic drugs and there were no other findings on examination. Lithium and olanzapine were discontinued and he was kept under observation. After 2 days his pulse rate was 62/minute without any intervention. Considering that lithium-induced sinus bradycardia occurred at therapeutic range, he was started on sodium valproate 1000 mg/day along with oral haloperidol 10 mg/day. There was improvement in manic symptoms without any cardiac side-effects.

DISCUSSION

In our patient, the discontinuation of lithium therapy without any other specific intervention resulted in the recovery of normal function of the sinoatrial node. The appearance of bradycardia after introduction of lithium and subsequent recovery following discontinuation confirmed the relationship between lithium and sinus node dysfunction. Although the patient was also receiving olanzapine, the possibility of sinus node dysfunction due to olanzapine is minimal.[7] There are rare reports of bradycardia associated with olanzapine in elderly patients,[8,9] and only a single report implicating olanzapine in a healthy volunteer.[10] Therefore, olanzapine is less likely to be the offending agent in our case, a young adult, and it is probable that lithium might be the causal agent.

The true prevalence of lithium-induced sinus node dysfunction is not known. Hagman[11] reported sinus node dysfunction in 2 of 97 patients screened using clinical examination, ECG and carotid massage. Most reported cases of lithium-induced sinus node dysfunction reversed following discontinuation of medication.[2,4] Nevertheless, there have been occasional reports of irreversible sinus node dysfunction induced by re-challenge with lithium.[12] Hence, we decided not to expose our patient to lithium again.

Lithium-induced cardiac toxicity has been hypothesized to occur because lithium enters the cardiac cells similar to sodium and its ineffective removal causes intracellular replacement of potassium.[13] Lithium decreases spontaneous depolarization of the sinus node and the conduction velocity in the atrioventricular and intraventricular conduction systems.[13] Other mechanisms include the reduction of adrenergic response and interference with calcium influx in the pacemaker cells of the sinus node.[13] Also, lithium-associated bradyarrhythmias have been linked to lithium-induced hypercalcaemia and hypothyroidism.[14] Further, patients who develop sinus node dysfunction may have subclinical structural or

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functional sinus node dysfunction that is unmasked by lithium-induced block of cardiac sodium channels, as evidenced by unmasking of Brugada syndrome with lithium therapy.[15]

In summary, this case shows that cardiotoxicity of lithium can occur even with lithium levels in the therapeutic range. Therefore, patients receiving lithium should have their pulse monitored regularly for any rhythm abnormalities and lithium should be discontinued if rhythm disturbances occur during treatment. Further, patients should preferably not be re-challenged with lithium because of the possibility of recurrence of bradycardia and the potential for irreversibility.

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