CASE REPORT

Lithium-induced sinus node dysfunction at therapeutic levels

Ranjan K Shetty,¹ G Vivek,¹ Amrita Parida,² Shashikanth Chetty²

¹Department of Cardiology, Kasturba Medical College, Manipal, Karnataka, India
²Department of Pharmacology, Kasturba Medical College, Manipal, Karnataka, India

Correspondence to
 Dr G Vivek,
 vivekgraman@gmail.com

SUMMARY

Lithium is used as an antimanic and mood-stabilising drug. It can cause various adverse effects such as nausea, vomiting, polyuria, fine tremors, myocarditis and arrhythmias. We are describing a case of lithium induced sinus-node dysfunction in a patient with serum lithium levels in therapeutic range.

BACKGROUND

Lithium, a small monovalent cation, is used as an antimanic and mood-stabilising drug. The exact mechanism of its mood-stabilising action is not known. Its main effect is probably inhibition of hydrolysis of inositol phosphate, uncoupling of receptors from G-proteins or alteration of various neurotransmitters. Adverse effects of lithium include nausea, vomiting, fine tremors, goitre, diabetes insipidus, diarrhoea, constipation, weight gain etc.¹ Occasionally, lithium may cause myocarditis, ventricular arrhythmias and sinus-node dysfunction.² In addition, T-wave flattening and inversion may be seen in electrocardiogram. We hereby describe a case of lithium-induced sinus-node dysfunction occurring in a patient who was on lithium for 15 years for bipolar disorder and whose serum lithium levels were in therapeutic range.

CASE PRESENTATION/INVESTIGATIONS

A 46-year-old female came to the emergency department with complaints of giddiness since 3 days. On examination, she had an irregularly irregular pulse with rate of 45/min, and blood pressure of 90/60 mm Hg. Her electrocardiogram was suggestive of sinus arrest with intermittent junctional escape (figure 1). Echocardiogram showed normal left ventricular function (ejection fraction 75%). Serum electrolytes and thyroid-stimulating hormone levels were within normal limits.

Treatment history revealed that she was on lithium therapy (450 mg BD) for the past 15 years. She had no history, or family history, of heart disease and she was not on any other medication known to cause heart block. Her serum lithium level (0.7 mmol/l) was within therapeutic range.

DIFFERENTIAL DIAGNOSIS

Lithium induced sinus-node dysfunction or idiopathic sick sinus syndrome (SSS). SSS was ruled out as her rhythm reverted to sinus with a regular heart rate on the cessation of lithium therapy.

TREATMENT

Based on drug history and investigations, the patient was diagnosed as a case of lithium-induced sinus-node dysfunction. Lithium was stopped and a temporary pacemaker was placed in the right ventricle, via the femoral route. Sinus-node function improved over the next 3 days (figure 2). Pre-discharge Holter study revealed sinus arrhythmia without any prolonged pauses. She was then started on divalproex sodium 250 mg twice a day and quetiapine 25 mg once a day and discharged after 5 days.

OUTCOME AND FOLLOW-UP

She is asymptomatic at 1-month follow-up, with a resting heart rate of 74/min.

DISCUSSION

The safety and efficacy of lithium salts for the treatment of mania and major depression associated with bipolar illness is well established. Conduction defects such as sinus-node dysfunction, atrioventricular block, right bundle branch block and left anterior hemiblock have been associated with chronic lithium treatment.^{2–6} Lithium-induced sinus-node dysfunction usually occurs at toxic levels and rarely at therapeutic levels (0.6–1.2 mEq/l) (table 1).

Figure 1 ECG showing bradycardia with intermittent prolonged pauses (horizontal blue lines).

To cite: Shetty RK, Vivek G, Parida A, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-008107

Figure 2 ECG showing sinus bradycardia (HR=55/min) with no pauses.

Various mechanisms have been proposed for lithium-induced sinus-node dysfunction. It causes hypercalcemia, hypothyroidism and a decrease in intracellular potassium levels. These disturbances seem to induce various electrophysiological changes, including decrease in the depolarisation rate and electrical impulse propagation.^{7–9} Lithium also blocks the voltage-gated sodium channels which have an important role in the myocardial conduction velocity as well as the sinus-node pacemaker activity.^{10–11} It causes a concentration-dependent block of the peak sodium current, with the concentration required for 50% inhibition being $6.8 \pm 0.4 \mu\text{M}$.¹² The pacemaker (HCN2/4) channels, L-type calcium channels, acetylcholine-gated potassium channels and the sodium–calcium exchanger control the pacemaker activity of sinus node.^{13–15} As lithium interferes with their activities, it affects the sinus-node function.^{14–16} The fact that not all patients on lithium therapy develop sinus-node dysfunction suggests that there may be other factors accentuating conduction defects. Fluctuations in serum levels of lithium,^{5–8} intrinsic cardiac parasympathetic and sympathetic tone,¹⁷ age-related interstitial fibrosis and decrease in sinus rate,¹⁸ variations in cardiac sodium channel expression¹⁹ and underlying pre-existing cardiac diseases¹² are some of such factors.

The above case was assessed for causality by use of the WHO-UMC system. Dechallenge led to abatement of symptoms; no rechallenge was done. This adverse drug reaction can be categorised as ‘probable/likely’.²⁰

Learning points

- Symptomatic sinus-node dysfunction, though rare, can occur at therapeutic levels of lithium in predisposed individuals.
- Treatment essentially involves withdrawal of the drug and temporary haemodynamic support during the symptomatic phase.
- Hence, physicians and psychiatrists treating patients with lithium for a prolonged time need to be cautious about the same.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th edn. New York: McGraw-Hill Companies, 2011:445–7.
- 2 Wilson JR, Kraus ES, Bailas MM, et al. Reversible sinus-node abnormalities due to lithium carbonate therapy. *N Engl J Med* 1976;294:1223–4.
- 3 Riccioni N, Roni P, Bartolomei C. Lithium-induced sinus node dysfunction. *Acta Cardiol* 1983;38:133–8.

Table 1 Association between symptomatic sinus-node dysfunction and therapeutic serum lithium levels²¹

Age/sex	Dosage (mg/day)	Duration	Serum lithium level (mM)	Arrhythmia
44/Female	1200	3 years	1	Sinoatrial block
56/Female	1000	5 years	1	Sinoatrial block
75/Female	660	2 years	0.3	Sinus bradycardia with arrest and JER
63/Male	NA	6 years	1.1	Sinus bradycardia with asystole
69/Female	600	10 years	1.1	Sinus bradycardia with JER
53/Female	NA	1 month	0.71	Sinus pauses with JER
59/Female	750	6 years	0.1–1.3	Sinus-node escape with JER and ventricular bigeminy
60/Male	750	5 years	0.6–1.15	Sinus bradycardia
56/Male	NA	14 years	0.5–0.9	Sinus bradycardia
64/Male	1200	11 years	0.72	Sinus-node arrest with idioventricular escape rhythm

JER, Junctional escape rhythm; NA, Not available.

- 4 Farag S, Watson RD, Honeybourne D. Symptomatic junctional bradycardia due to lithium intoxication in patient with previously normal electrocardiogram. *Lancet* 1994;343:1371.
- 5 Moltedo JM, Porter GA, State MW, *et al.* Sinus node dysfunction associated with lithium therapy in a child. *Tex Heart Inst J* 2002;29:200–2.
- 6 Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry* 1985;30:114–16.
- 7 Wolf ME, Ranade V, Molnar J, *et al.* Hypercalcemia, arrhythmia, and mood stabilizers. *J Clin Psychopharmacol* 2000;20:260–4.
- 8 Livingstone C, Rampes H. Lithium: A review of its metabolic adverse effects. *J Psychopharmacol* 2006;20:347–55.
- 9 Singer I, Rotenberg D. Mechanisms of lithium action. *N Engl J Med* 1973;289:254–60.
- 10 Maier SK, Westenbroek RE, Yamanushi TT, *et al.* An unexpected requirement for brain-type sodium channels for control of heart rate in the mouse sinoatrial node. *Proc Natl Acad Sci USA* 2003;100:3507–12.
- 11 George AL Jr. Inherited disorders of voltage-gated sodium channels. *J Clin Invest* 2005;115:1990–9.
- 12 Darbar D, Yang T, Churchwell K, *et al.* Unmasking of brugada syndrome by lithium. *Circulation* 2005;112:1527–31.
- 13 Boyett MR, Honjo H, Kodama I. The sinoatrial node, a heterogeneous pacemaker structure. *Cardiovasc Res* 2000;47:658–87.
- 14 Bogdanov KY, Vinogradova TM, Lakatta EG. Sinoatrial nodal cell ryanodine receptor and Na(+)-Ca(2+) exchanger: molecular partners in pacemaker regulation. *Circ Res* 2001;88:1254–8.
- 15 Biel M, Schneider A, Wahl C. Cardiac HCN channels: structure, function, and modulation. *Trends Cardiovasc Med* 2002;12:206–12.
- 16 Azene EM, Xue T, Li RA. Molecular basis of the effect of potassium on heterologously expressed pacemaker (HCN) channels. *J Physiol* 2003; 547:349–56.
- 17 Perini R, Veicsteinas A. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. *Eur J Appl Physiol* 2003;90:317–25.
- 18 Opthof T. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc Res* 2000;45:173–6.
- 19 Bezzina CR, Shimizu W, Yang P, *et al.* Common sodium channel promoter haplotype in asian subjects underlies variability in cardiac conduction. *Circulation* 2006;113:338–44.
- 20 The use of the WHO-UMC system for standardized case causality assessment (monograph on the internet) Uppsala: the Uppsala monitoring centre. 2005. <http://who-umc.org/Graphics/24734.pdf> (accessed on 31 Jul 2012).
- 21 Oudit GY, Korley V, Backx PH, *et al.* Lithium-induced sinus node disease at therapeutic concentrations: Linking lithium-induced blockade of sodium channels to impaired pacemaker activity. *Can J Cardiol* 2007;23:229–32.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow