Lithium-induced sinus node disease at therapeutic concentrations: Linking lithium-induced blockade of sodium channels to impaired pacemaker activity

Gavin Y Oudit MD PhD FRCPC^{1,2}, Victoria Korley MD FRCPC¹, Peter H Backx DVM PhD², Paul Dorian MD FRCPC¹

GY Oudit, V Korley, PH Backx, P Dorian. Lithium-induced sinus node disease at therapeutic concentrations: Linking lithium-induced blockade of sodium channels to impaired pacemaker activity. *Can J Cardiol* 2007;23(3):229-232.

The present report describes a case of sinus node arrest in a manic-depressive patient being treated with lithium carbonate with a therapeutic serum level of lithium. A permanent rate-modulated ventricular pacemaker was inserted and lithium therapy was continued. A review of literature revealed several other similar case reports in which both therapeutic and toxic levels of serum lithium levels were associated with sinus node dysfunction and bradyarrhythmias. Because lithium is a potent blocker of cardiac sodium channels, and given the critical importance of sodium channels in pacemaker activity, lithium-induced sodium channel blockade is likely an important mechanism in sinus node dysfunction.

Key Words: *Cardiac sodium channels; Lithium; Sinus node dysfunction*

We describe a 64-year-old man with a history of bipolar depression who was maintained on 1200 mg of lithium carbonate for 11 years, and presented with prolonged presyncope (45 min) associated with bradycardia and hypotension (blood pressure of 85/55 mmHg). He was not taking any atrioventricular (AV) node-blocking drugs. The 12-lead electrocardiogram showed sinus node arrest (Figure 1) with an idioventricular escape rhythm at 35 beats/min to 40 beats/min. He was treated with intravenous fluids and intravenous atropine, and his rhythm reverted to a normal sinus rhythm (Figure 2). His serum lithium was 0.72 mM, which was within the therapeutic range (0.5 mM to 1.5 mM). There was no known personal or family history of cardiovascular disease, syncope or sudden cardiac death. Levels of plasma creatine kinase (muscle-brain), troponin I, plasma electrolytes (including calcium), as well as renal function, were within normal limits. Thyroid function tests showed normal thyroid-stimulating hormone levels and free triiodothyronine and L-thyroxine levels. Chest x-ray was normal. An exercise Cardiolute (Bristol-Myers Squibb Medical Imaging, Inc, USA) stress test was performed to assess sinus and AV nodal response to exercise and to screen for coronary artery disease. The patient's heart rhythm at the start of the test was normal, as shown in Figure 2. During the stress test, the sinus rate increased appropriately to 140 beats/min with an exercise time of 12 min.

Un dysfonctionnement du nœud sino-auriculaire induit par du lithium à concentration thérapeutique : Un lien entre le blocage des canaux sodiques causé par le lithium et une altération de l'activité du stimulateur cardiaque

Le présent compte rendu décrit un cas d'arrêt du nœud sino-auriculaire chez un patient maniacodépressif traité au carbonate de lithium à un taux sérique thérapeutique de lithium. On a installé un stimulateur ventriculaire permanent à fréquence asservie et poursuivi le traitement. Une analyse bibliographique a révélé plusieurs autres déclarations de cas similaires dans lesquels à la fois les taux thérapeutique et toxique de lithium sérique s'associaient à un dysfonctionnement du nœud sino-auriculaire et à des bradyarythmies. Puisque le lithium est un puissant bloqueur des canaux sodiques cardiaques et étant donné l'importance critique des canaux sodiques dans l'activité du stimulateur cardiaque, le blocage des canaux sodiques induit par le lithium est probablement un mécanisme important dans le dysfonctionnement du nœud sino-auriculaire.

There were no diagnostic electrocardiographical changes, and myocardial perfusion was normal at rest and with exercise. A transthoracic echocardiogram showed normal left ventricular systolic function with normal aortic and mitral valvular function. A diagnosis of lithium-induced sinus node dysfunction was made based on the absence of other competing diagnoses and the similarity of indications in this case to those in other documented case reports, although the role of modifying factors (such as age-related changes in the sinoatrial [SA] node or high vagal tone) could not be ruled out. The patient has had suicidal ideation and previous suicide attempts associated with a reduced dose of lithium, which precluded us from withdrawing his lithium therapy. Given the high likelihood of a recurrence of the bradyarrhythmia, a rate-modulated ventricular pacemaker was implanted, and the patient was discharged on his preadmission dose of lithium carbonate.

DISCUSSION

Lithium salts were introduced for psychiatric use approximately 55 years ago to treat mania. Their use for this purpose was delayed until 1970, in part due to the uncontrolled use of lithium as a salt substitute and instances of toxicity in patients with cardiac disease (see below). Subsequently, the safety and efficacy of lithium salts for the treatment of mania and major depression associated with bipolar illness became

¹St Michael's Hospital; ²Heart and Stroke/Richard Lewar Centre of Excellence, University of Toronto, Toronto, Ontario
Correspondence: Dr Gavin Y Oudit, Room 68, 150 College Street, Heart and Stroke/Richard Lewar Centre of Excellence, Fitzgerald Building, University of Toronto, Toronto, Ontario M5S 3E2. Telephone 416-599-4257, fax 416-946-8380, e-mail gavin.oudit@utoronto.ca
Received for publication January 21, 2006. Accepted February 8, 2006

Figure 1) Twelve-lead electrocardiogram during the symptomatic phase showing sinus node arrest with an idioventricular escape rhythm at 35 beats/min to 40 beats/min

Figure 2) Twelve-lead electrocardiogram during the recovering phase showing normal sinus rhythm with normal PR interval, QRS duration and QTc interval

well established. Lithium-induced sinus node dysfunction ranging from benign to severe has been described at therapeutic (Table 1) and toxic serum levels (1-4) in both pediatric and adult patients. The conduction defects linked to lithium include sinus node dysfunction, AV block, right bundle branch block and left anterior hemiblock (1-6). The putative mechanisms of

lithium-associated bradyarrhythmias have been linked to lithium-induced hypercalcemia and hypothyroidism (6,7).

However, over the past decades, several case reports of sinus node dysfunction have been described in patients on lithium who were euthyroid and normocalcemic (Table 1) (8-14). An explanation for these observations is lacking. The recent

TABLE 1
Association between symptomatic sinus node dysfunction and therapeutic serum lithium levels

Age/sex	Dosage (mg/day)	Duration	Serum lithium level (mM)	Arrhythmia	Reference
44/Female	1200	3 years	1	Sinoatrial block	8
56/Female	1000	5 years	1	Sinoatrial block	9
75/Female	660	2 years	0.3	Sinus bradycardia with arrest and JER	10
63/Male	NA	6 years	1.1	Sinus bradycardia with asystole	10
69/Female	600	10 years	1.1	Sinus bradycardia with JER	11
53/Female	NA	1 month	0.71	Sinus pauses with JER	11
59/Female	750	6 years	0.1–1.3	Sinus node escape with JER and ventricular bigeminy	12
60/Male	750	5 years	0.6–1.15	Sinus bradycardia	13
56/Male	NA	14 years	0.5–0.9	Sinus bradycardia	14
64/Male	1200	11 years	0.72	Sinus node arrest with idioventricular escape rhythm	Present report

JER Junctional escape rhythm; NA Not available

demonstration that lithium can unmask Brugada syndrome has provided a crucial link to lithium-induced sinus node dysfunction (15). Indeed, lithium chloride caused a concentration-dependent block of the peak sodium current, with the concentration required for 50% inhibition being $6.8 \pm 0.4 \mu\text{M}$ (15), which is consistent with permeation in native voltage-gated sodium channels via a multi-ion mechanism (16). In addition to the well-established role of voltage-gated sodium channels as major determinants of myocardial conduction velocity (17,18), recent data have also provided strong evidence of a critical role for cardiac sodium channels in sinus nodal pacemaker activity. Sodium channels are expressed in the SA node (and surrounding tissue), and sinus node dysfunction caused by the failure of impulse generation (sinus arrest) or conduction into the adjacent atrial myocardium (exit block) has been linked to sodium channel mutations (17–20). Loss of function mutations in human cardiac sodium channels have been linked to atrial standstill (21), conduction system disease (22), sick sinus syndrome and bradyarrhythmia (19,20). Furthermore, a murine model with a partial loss of the pore-forming (alpha) subunits of the sodium channel essentially recapitulates the key features of sinus nodal dysfunction in humans (23).

Sinus nodal pacemaker activity is governed by the complex interaction between pacemaker (HCN2/4) channels, L-type calcium and acetylcholine-gated potassium channels, with a

potential contribution from the sodium-calcium exchanger (24–26). Lithium may also alter the sinus node pacing function by interacting with pacemaker (HCN) channels (27) and/or the sodium-calcium exchanger (25). Although pacemaker channels are nonspecific monovalent cation channels, under physiological conditions the inward pacemaker current is mainly driven by sodium ion permeation of the pacemaker channels (26). Lithium may also block the pacemaker sodium current, thereby impairing pacemaker activity of the SA nodal cells (26,27). The recognition that only a fraction of patients on lithium therapy will manifest sinus nodal dysfunction and its occurrence after a long time following the initiation of lithium therapy (Table 1) is consistent with a multifactorial mechanism for sinus nodal pacing activity, which implies that other intrinsic and/or extrinsic factors may also play an important role. These factors can include variation in serum levels of lithium (4,7), degree of cardiac parasympathetic and sympathetic tone (28), age-dependent accumulation of interstitial fibrosis and a decrease of intrinsic sinus rate (due to reduction of the pacemaker current [29]) and/or interindividual variation of the cardiac sodium current (due to variable sodium channel expression [30]). Patients who develop sinus node dysfunction may have subclinical structural or functional sinus node dysfunction that is unmasked by lithium-induced block of cardiac sodium channels.

REFERENCES

- Wilson JR, Kraus ES, Bailas MM, Rakita L. Reversible sinus-node abnormalities due to lithium carbonate therapy. *N Engl J Med* 1976;294:1223–4.
- Riccioni N, Roni P, Bartolomei C. Lithium-induced sinus node dysfunction. *Acta Cardiol* 1983;38:133–8.
- Farag S, Watson RD, Honeybourne D. Symptomatic junctional bradycardia due to lithium intoxication in patient with previously normal electrocardiogram. *Lancet* 1994;343:1371.
- Molledo JM, Porter GA, State MW, Snyder CS. Sinus node dysfunction associated with lithium therapy in a child. *Tex Heart Inst J* 2002;29:200–2.
- Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry* 1985;30:114–6.
- Wolf ME, Ranade V, Molnar J, Somberg J, Mosnaim AD. Hypercalcemia, arrhythmia, and mood stabilizers. *J Clin Psychopharmacol* 2000;20:260–4.
- Livingstone C, Rampes H. Lithium: A review of its metabolic adverse effects. *J Psychopharmacol* 2006;20:347–55.
- Liem KS, van der Does de Willebois JA. [Electrocardiographical changes during lithiumcarbonate therapy.] *Ned Tijdschr Geneesk* 1975;119:1509–12.
- Wellens HJ, Cats VM, Duren DR. Symptomatic sinus node abnormalities following lithium carbonate therapy. *Am J Med* 1975;59:285–7.
- Hagman A, Arnman K, Ryden L. Syncope caused by lithium treatment. Report on two cases and a prospective investigation of the prevalence of lithium-induced sinus node dysfunction. *Acta Med Scand* 1979;205:467–71.
- Roose SP, Nummerger JJ, Dunner DL, Blood DK, Fieve RR. Cardiac sinus node dysfunction during lithium treatment. *Am J Psychiatry* 1979;136:804–6.
- Rodney WM, Chopivsky P, Hara JH. Lithium-induced dysrhythmias as a marker for sick sinus syndrome. *J Fam Pract* 1983;16:797–9.
- Weintraub M, Hes JP, Rotmensch HH, Soferman G, Liron M. Extreme sinus bradycardia associated with lithium therapy. *Isr J Med Sci* 1983;19:353–5.
- Montalescot G, Levy Y, Farge D, et al. Lithium causing a serious sinus-node dysfunction at therapeutic doses. *Clin Cardiol* 1984;7:617–20.
- Darbar D, Yang T, Churchwell K, Wilde AA, Roden DM. Unmasking of brugada syndrome by lithium. *Circulation* 2005;112:1527–31.

16. Favre I, Moczydlowski E, Schild L. On the structural basis for ionic selectivity among Na⁺, K⁺, and Ca²⁺ in the voltage-gated sodium channel. *Biophys J* 1996;71:3110-25.
17. 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.
18. George AL Jr. Inherited disorders of voltage-gated sodium channels. *J Clin Invest* 2005;115:1990-9.
19. Veldkamp MW, Wilders R, Baartscheer A, Zegers JG, Bezzina CR, Wilde AA. Contribution of sodium channel mutations to bradycardia and sinus node dysfunction in LQT3 families. *Circ Res* 2003;92:976-83.
20. Benson DW, Wang DW, Dymont M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest* 2003;112:1019-28.
21. Groenewegen WA, Firouzi M, Bezzina CR, et al. A cardiac sodium channel mutation cosegregates with a rare connexin40 genotype in familial atrial standstill. *Circ Res* 2003;92:14-22.
22. Tan HL, Bink-Boelkens MT, Bezzina CR, et al. A sodium-channel mutation causes isolated cardiac conduction disease. *Nature* 2001;409:1043-7.
23. Lei M, Goddard C, Liu J, et al. Sinus node dysfunction following targeted disruption of the murine cardiac sodium channel gene *Scn5a*. *J Physiol* 2005;567:387-400.
24. Boyett MR, Honjo H, Kodama I. The sinoatrial node, a heterogeneous pacemaker structure. *Cardiovasc Res* 2000;47:658-87.
25. 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.
26. Biel M, Schneider A, Wahl C. Cardiac HCN channels: Structure, function, and modulation. *Trends Cardiovasc Med* 2002;12:206-12.
27. 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.
28. 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.
29. Opthof T. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc Res* 2000;45:173-6.
30. 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.