Chronic lithium intoxication: Varying electrocardiogram manifestations

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Abstract:
Lithium is a commonly used drug in psychiatric practice. It is used in the treatment of depression and bipolar disorder. It has a narrow therapeutic index with documented adverse effects even near therapeutic levels. It has myriad of manifestations at toxic levels. The cardiovascular effects range from relatively benign ST-T wave changes to fatal arrhythmias. We describe a case of lithium toxicity which presented as a junctional rhythm and later showed a variety of manifestations such as complete heart block, atrial fibrillation, sinus bradycardia, and finally reverted to sinus rhythm at par with serum lithium levels.

Key words:
Arrhythmias, electrocardiography, lithium toxicity

Lithium is a commonly used drug in routine psychiatric practice for a variety of conditions such as depressive and bipolar affective disorders. However, lithium has a low safety profile in view of its narrow therapeutic index and adverse effect profile. It is known to cause adverse effects even at therapeutic levels. Here, we would like to describe a case of bipolar disorder, a 77-year-old hypertensive and hypothyroid female who was on chronic lithium therapy who presented with ataxia, tremor, and giddiness. Her initial electrocardiogram (ECG) on arrival in emergency department showed junctional rhythm. During the course of her illness, she developed atrial fibrillation, complete heart block, sinus bradycardia, and finally spontaneously reverted to sinus rhythm. Her laboratory reports were suggestive of lithium toxicity with serum lithium levels in toxic range. She responded to conservative management with gradual decline in serum lithium levels and cardiac rhythm reverting to sinus rhythm.

Case Report
A 77-year-old female, known case of bipolar affective disorder, hypertension, and hypothyroidism, presented to emergency department with a history of giddiness, swaying while walking, and involuntary rhythmic movement of hands. Detailed drug history revealed that she was on 600 mg lithium/day, in two divided doses for 30 years. Other drugs included 25 mg losartan and 25 mg metoprolol for hypertension and 12.5 mcg of levothyroxine supplementation. On examination, she had a pulse rate of 38/min which was regular with hypotension; jugular venous pressure was elevated with prominent ‘a’ wave. She was conscious, coherent, oriented and was found to have coarse tremors and ataxia. There were no other focal neurological deficits. Cardiovascular system examination was within normal limits. Other systemic examination was unrevealing.

The initial ECG done in the emergency department showed junctional rhythm [Figure 1a]. Echocardiographic evaluation was done in view of sudden hypotension which was normal. On day 1 of admission, laboratory values showed serum lithium levels of 2.6 mmol/L (normal range - 0.5–1 mmol/L) with creatinine of 1.6 mg/dl. Thyroid-stimulating hormone (TSH) level was in therapeutic range, and other laboratory parameters including serum sodium were in normal limits. In view of symptomatic bradycardia, temporary pacemaker was inserted. Lithium, losartan, and metoprolol were withheld, and she was hydrated aggressively with normal saline. On day 2 of admission, serum lithium level was 2.1 mmol/L, and repeat value after 12 h showed a level of 1.8 mmol/L. ECG revealed atrial fibrillation with controlled ventricular rate which was managed conservatively with rate control drugs [Figure 1b]. Nephrology consultation was sought; hemodialysis was deferred in view of improving renal functions.

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and serial decrease in lithium levels. On day 3, the patient developed complete heart block at serum lithium levels of 1.4. On day 4 [Figure 1c], lithium level was 0.9, and she reverted spontaneously to sinus rhythm with bradycardia and finally rate normalized. Temporary pacemaker was removed as her serum lithium levels came down to therapeutic levels. In view of elderly age and documented cardiotoxic effects, lithium was totally stopped, and valproate was started. She tolerated valproate well. Her antihypertensives were restarted, and she was discharged.

With a score of 5 with Naranjo algorithm for causality assessment, lithium had a probable causal association with the adverse drug event. The adverse drug reaction was severe as assessed by the Hartwig’s severity assessment scale (score = 5).

Discussion

Lithium is a widely used drug for bipolar affective disorder, depression, and schizoaffective disorder. Great amount of caution should be exercised while using it in view of narrow therapeutic index and multisystem toxicity profile. It is advisable to initiate lithium only if facilities for monitoring serum lithium levels are available. Clinical profile of intoxication includes mild intoxication producing diarrhea, vomiting, coarse hand tremor, and muscle weakness; moderate intoxication characterized by nystagmus, ataxia, myoclonus, and confusion, and severe degree of intoxication causing seizures, impaired consciousness, coma, and death.[3]

Lithium interacts with thyroid and results in a variety of manifestations such as hypothyroidism, goiter, and autoimmune thyroiditis. Hypothyroidism is a well-documented endocrine disorder seen in chronic lithium toxicity. Thyroid follicular cells avidly absorb lithium; the absorbed lithium prevents the release of thyroid hormones from thyroglobulin. It also decreases the sensitivity of thyroid follicular cells to TSH, thus resulting in hypothyroidism. It can sometimes result in goiter as follicular cells are stimulated by raising thyroid-stimulating hormone levels secondary to hypothyroidism. In our case, the patient received lithium therapy for almost 30 years, which might have caused hypothyroidism.

Lithium has good oral bioavailability. After oral ingestion, peak blood levels reach within one to 2 h. It has a half-life of 18 h in adults and 36 h in elderly, which might be secondary to reduced glomerular filtration rate in elderly. It is nonprotein bound and is freely distributed throughout total body water. It is freely filtered by the kidney with 60% reabsorbed in the proximal tubule. Drugs which cause volume depletion and renal impairment such as diuretics and angiotensin-converting-enzyme inhibitors can increase reabsorption of lithium.[2] In our case, the patient is on losartan which is an angiotensin-receptor blocker having action similar to angiotensin-converting-enzyme inhibitors which might have precipitated lithium toxicity.

Serious cardiac arrhythmias are rarely seen in lithium toxicity. The cardiac manifestations of lithium toxicity include junctional rhythm, atrial fibrillation, ST-T wave changes, supraventricular tachycardia, and sinus node arrest. Cardiac effects of lithium are seen at wide range of lithium levels at both therapeutic and toxic levels. Its manifestations range from benign ST-segment, T-wave changes to severe manifestations such as sinus node dysfunction, atrial flutter, atrioventricular blocks, left anterior hemiblock, right bundle branch block, ventricular tachycardia, ventricular fibrillation, and sudden cardiac arrest.[3]

Several mechanisms have been proposed to explain the conduction system disturbances caused by lithium. Lithium being a monovalent cation competes with cation such as sodium, potassium, and magnesium and can cause electrolyte disturbances. It interferes with Na-Ca exchanger and Na/K pump resulting in disturbances of membrane physiology. It can cause hypercalcemia, decrease intracellular potassium, thus interfering with impulse propagation and depolarization which manifests as ST, T changes on ECG. It was proposed that lithium interfering with potassium can cause intracellular hypokalemia and extracellular hyperkalemia.[4] This intracellular hypokalemia in the atrium is proposed to be etiological factor for atrial arrhythmias. The sensitivity of sinus node to sympathetic stimulated is decreased by blockade of voltage-gated sodium channels resulting in sinus arrest. Lithium-induced sinus node dysfunction might have caused the junctional rhythm in our case.

Figure 1: (a) 12-lead electrocardiogram showing heart rate of 38 bpm with the absence of P waves suggesting junctional rhythm (b) 12-lead electrocardiogram with heart rate of 74 bpm with irregular RR intervals and fibrillatory P waves suggestive of atrial fibrillation with controlled ventricular rate (c) 12-lead electrocardiogram with heart rate of 44 bpm with atrioventricular dissociation suggestive of complete heart block
Lithium is nonprotein bound and is freely distributed throughout the body. Lithium is easily dialyzable; however, its role in the treatment of acute on chronic lithium toxicity is questionable. Patients on chronic lithium therapy have lithium stored in intracellular compartment, thus even if lithium is removed by hemodialysis intracellular lithium will diffuse into extracellular compartment till a new equilibrium is established; thus, the removal of extracellular lithium by dialysis does not affect the blood levels much in view of rebound of lithium concentration in chronic lithium toxicity lithium.[9] In our case, dialysis was deferred in view of chronic history of lithium consumption and was managed conservatively with adequate hydration. Serum lithium concentrations normalized, and the patient had reverted spontaneously to sinus rhythm.

Conflicts of Interest
There are no conflicts of interest.

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