Lithium Intoxication with Sinus Node Dysfunction: Report of a Case

SHU-PING CHAO¹, HUEY-MING LO¹,²

Lithium has been reported to cause many cardiac side effects, such as T wave flattening, ST segment abnormalities, QT prolongation, bradycardia, wide-complex tachycardia, junctional rhythm, heart block, Brugada-like change, and sinus node dysfunction. We report a 34-year-old woman who was diagnosed bipolar affective disorder and treated with lithium for 2 years. She was brought to our hospital due to changes of behavior and cognitive function. Electrocardiogram revealed sinus node dysfunction. Drug screen showed a toxic level of lithium. She was treated with temporary pacing and continuous venovenous hemofiltration and recovered uneventfully. Because of its narrow therapeutic index, lithium intoxication may occur in chronic treated patients. This case report reminds clinical physicians about the possible complications of lithium therapy and should be used with great caution.

Key words: lithium intoxication; sinus node dysfunction

Introduction

Lithium has been widely used in treatment of bipolar disorder. Because of its narrow therapeutic index, lithium intoxication may occur in chronic treated patients. Electrocardiographic changes of lithium intoxication have been reported, including T wave flattening (1-3), ST segment abnormalities (1-3), QT prolongation (2,3), bradycardia (1,3), wide-complex tachycardia (4), junctional rhythm (1), heart block (1,5), Brugada-like change (6), and sinus node dysfunction (7-11). In this case report, we present a victim of bipolar affective disorder who developed sinus node dysfunction with a toxic plasma level of lithium.

Case Report

This patient is a 34-year-old woman who was diagnosed bipolar affective disorder for 2 years. The medications she took before admission were as followings: lithium 1200mg/day, escitalopram 20mg/day, quetiapine 200mg/day, topiramate 300mg/day, and estazolam 3mg/day.

She was admitted due to changes in behavior and cognitive function. Bradyarrhythmia was noted on admission. Initial electrocardiogram revealed marked bradycardia, sinus pause, and inverted T waves (Fig. 1). Another electrocardiogram was performed later and showed junctional rhythm (Fig. 2). Laboratory data showed normal white blood cell count, anemia (hemoglobin: 8.7gm/dl), elevated blood urea nitrogen (27mg/dl) and plasma creatinine (2.6mg/dl), hyperkalemia (6.3mEq/L), and mildly elevated magnesium level (2.9mg/dl). Drug screening test showed that the plasma lithium concentration was 5.93meq/L (therapeutic range, 0.6-1.5mEq/L) and plasma benzodiazepine concentration was over 200ng/mL (normal range,
Lithium and sinus node dysfunction

0-3ng/mL). Besides, her thyroid function was normal.

Under the impression of lithium intoxication with sinus node dysfunction, she was transferred to intensive care unit for further management with temporary pacemaker pacing and continuous venovenous hemofiltration. The plasma potassium concentration was corrected to normal range. Electrocardiogram revealed normal sinus rhythm on the 5th day of hospitalization. The plasma lithium concentration dropped to 0.63mEq/L on the same day. We kept following the plasma lithium concentration and found no rebound of concentration. Therefore, continuous venovenous hemofiltration was terminated and temporary pacemaker was removed. Her renal function also showed improvement after termination of renal replacement therapy. The plasma creatinine value dropped from 2.6mg/dl to 1.4mg/dl. Her urine output was excellent. She was discharged one month later due to an intercurrent bacteremia. The electrocardiogram remains normal since then.

**Discussion**

Lithium intoxication may occur in patients with long-term treatment because of a narrow therapeutic index (0.6-1.5mEq/L)\(^{(1-3,12)}\). The most common manifestation of lithium toxicity is altered mental status\(^{(2)}\). Besides, lithium has other adverse effects on renal, thyroid, and cardiac systems\(^{(1-3,13)}\).

Lithium intoxication is characterized primarily by neuromuscular hyperexcitability and central nervous system dysfunction\(^{(1)}\). Other neurological
symptoms include tremor, increased muscle tone and rigidity, drowsiness, apathy, sluggishness, ataxia, fasciculations, and stupor\(^{(1-3)}\). Most of these neurotoxicities are transient, and show improvement as the lithium toxicity resolves\(^{(1)}\).

Many lithium induced renal abnormalities have been described, including decreases in creatinine clearance, oliguria or polyuria, renal tubular acidosis, decreased urinary concentrating ability, and nephrotic syndrome\(^{(1-3)}\). Diabetes insipidus and hypernatremia may occur in 20% patients after lithium treatment\(^{(1,2)}\). This diabetes insipidus is not responsive to vasopressin and is nephrogenic in origin\(^{(1)}\).

Hypothyroidism has been reported in 1% to 20% in patients treated with lithium\(^{(1,2,13)}\). Lithium concentrates in the thyroid gland, achieving concentrations four to five times those occurring simultaneously in the plasma\(^{(1)}\). Normally, the thyroid response to thyroid-stimulating hormone is mediated by cAMP\(^{(1)}\). The formation and the action of cAMP are inhibited by lithium and lead to hypothyroidism\(^{(1)}\).

Increase in myocardial lithium level may lower intracellular potassium concentrations, causing T wave flattening and ST segment abnormalities\(^{(1,3)}\). Other electrocardiographic changes including QT prolongation\(^{(2,3)}\), bradycardia\(^{(1,3)}\), wide-complex tachycardia\(^{(9)}\), junctional rhythm\(^{(1)}\), heart block\(^{(1,5)}\), Brugada-like change\(^{(6)}\), and sinus node dysfunction\(^{(7-11)}\), have been reported. Lithium induced myocarditis and teratogenicity resulting in Ebstein’s anomaly have also been reported\(^{(1,2,4)}\).

The mechanism of how lithium suppresses sinus node is not well understood. Interaction between lithium and several currents such as \(I_{K1}\), \(I_{Ca}\), the \(Na^+/Ca^{2+}\) exchange current, and a \(H^+/K^+\) pump current might lead to the observed results\(^{(7)}\). Decreased sensitivity of sinus node to sympathetic stimulation induced by lithium may also play a role\(^{(7)}\). There was a literature proposed that sinus node dysfunction induced by lithium may be involved in the mechanism of lithium-induced hypothyroidism\(^{(9)}\). In one previous report of lithium intoxication, an invasive electrophysiologic study revealed marked prolongation of the corrected sinus node recovery time. The corrected sinus node recovery time shortened after plasma lithium concentration was corrected to normal range\(^{(9)}\). Most patients recover after discontinuation of lithium therapy. In rare instances, irreversible sinus node dysfunction may occur\(^{(10)}\).

In addition to a toxic level of lithium, the patient also had hyperkalemia and a high concentration of benzodiazepine. It is well known that hyperkalemia has many effects on cardiac tissue and changes on electrocardiogram. However, hyperkalemia induced sinus node dysfunction is rarely reported. In animal model, hyperkalemia up to 8.5mEq/L produces a gradual prolongation of the sino-crista terminalis interval\(^{(14)}\). Hyperkalemia between 8.5 to 10.0mEq/L produces arrest of most of the atria but persistence of electrical activity of the sinus node, crista terminalis, Bachmann bundle, His bundle and ventricles, and sustained sino-ventricular conduction\(^{(14)}\). Hyperkalemia may have very little effect on sinus nodal function or may induce sinus node dysfunction at very high level. Benzodiazepine related sinus node dysfunction has never been described previously.

The treatment of lithium intoxication requires aggressive management of patient’s airway and circulatory support, depending on clinical severity\(^{(1,2)}\). Because lithium clearance depends on glomerular filtration rate, fluid resuscitation is important to normalize the patient’s volume status and to establish normal urine output\(^{(1,2)}\). Renal replacement therapy such as hemodialysis and hemofiltration can help to enhance elimination rate\(^{(1,2,12)}\). Lithium is well cleared by hemodialysis with clearances of 63 to 170mL/min\(^{(1,2,12)}\). A rebound in plasma lithium concentration is frequently noted after termination of hemodialysis\(^{(1,2,12)}\). This rebound is a consequence of lithium diffusional flux-down from peripheral
tissues to the vascular compartment\(^{(1,2,12)}\). Therefore, plasma lithium concentration should be checked frequently after termination of hemodialysis\(^{(2)}\). Continuous renal replacement therapies have less clearance rate than hemodialysis, but can be used in patients with unstable hemodynamic status who cannot tolerate hemodialysis\(^{(1,2)}\). The continuous nature of these techniques decreases the possibility of rebound in plasma lithium concentration\(^{(2)}\).

The most common risk factor of lithium intoxication is volume depletion\(^{(1,2)}\). It is important to maintain normal volume status of patients who were treated with lithium\(^{(1,2)}\). There are some medications may influence on lithium concentrations, such as angiotensin-converting enzymes inhibitors, loop diuretics and thiazides, nonsteroidal anti-inflammatory drugs\(^{(1,2,15)}\). Concomitant use of these medications should be very cautious. In this case report, the patient took excessive dosage of medications because of suicide intention. Watery diarrhea for several days before admission was also noted. These are the possible reasons why she got lithium intoxication.

In summary, lithium is well known to induce sinus node dysfunction. Further studies designed to understand the mechanism of sinus node dysfunction are warranted. Great caution is needed when caring patients with long-term treatment of lithium.

References

鋰中毒與竇房結功能異常：病例報告

趙書平¹  駱惠銘¹,²

鋰已知會造成許多心室方面的副作用，例如T波平坦，ST段異常，QT間距延長，心搏過慢，寬的QRS頻脈，交界性節律，心室傳導阻礙，類似Brugada的變化，以及竇房結功能異常。我們報告一位三十四歲的女士，她被診斷為雙極性情感障礙，同時已經接受了兩年的鋰治療。她因為行為和認知功能的改變而被帶來我們醫院。心電圖顯示出竇房結功能異常。藥物檢測發現過量的鋰濃度。於是她接受了暫時性心室節律器之使用，以及連續性全靜脈血液過濾透析術的治療。經由透析治療，我們將鋰的濃度矯正至正常範圍，這位女士的竇房結功能也同時恢復正常。這份病例報告可以提醒所有臨床醫師對於鋰治療可能造成的副作用，同時也提醒大家在使用鋰時要特別小心。

關鍵詞：鋰中毒，竇房結功能異常

---

收件：97年5月30日 接受刊載：97年12月11日  
¹新光吳火獅紀念醫院心臟內科  ²輔仁大學醫學系  
通訊及插印本索取：駱惠銘醫師  臺北市士林區文昌路95號  新光吳火獅紀念醫院心臟內科  
電話：(02)28332211轉2084  傳真：(02)28369133
E-mail: m006459@ms.skh.org.tw