

Diagnostic and Therapeutic Challenges in Acute Lithium Intoxication: A Case Report

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ABSTRACT

Diagnostic and therapeutic challenges in acute lithium intoxication: a case report

Lithium (Li) is a highly efficient therapy in bipolar disorder, but its therapeutic index is extremely narrow. The vast majority of patients receiving maintenance Li therapy become toxic at some point during their course of treatment. Due to its pharmacokinetics, the clinical effects of Li toxicity vary according to the type of intoxication; and diagnosis may be difficult. We present a case of lithium intoxication in whom, despite very high serum Li levels, the clinical presentation was very subtle and we discuss treatment strategies in line with literature. A 37 year old female bipolar patient with a serum Li concentration of 5.4 mmol/L had insomnia, nausea and fine tremor which developed in the last three days. She had been on Li carbonate 1200 mg/day for the last 10 days. She recovered and her Li level returned to normal in 24 hours with forced alkaline diuresis and supportive measures. Lithium carbonate is applied in psychiatry in doses close to the maximum intake level. In some cases of Li intoxication, serum Li levels may be normal. Conversely, in acute overdoses because of Li's delayed serum equilibrium concentration may be very high, but because of normal intracellular concentrations, the patient may be asymptomatic. Clinical symptoms correlate best with severity of intoxication. Our case supports the approach that decisions regarding treatment in Li toxicity should be based on clinical parameters rather than Li levels.

Key words: Lithium, acute intoxication, adverse effects

ÖZET

Akut lityum zehirlenmesinde tanı ve tedavi güçlükleri: Olgu sunumu

Lityumun (Li) bipolar bozukluk tedavisinde etkinliği kanıtlanmış olmakla birlikte, terapötik indeksi çok dardır. İdam Li tedavisi alan hastaların çoğunda, tedavi sürecinde bir noktada toksisite oluşur. Lityumun farmakokinetik özellikleri nedeniyle, intoksikasyon tipine göre klinik belirtiler farklılıklar gösterir. Bu nedenle de, toksisitenin tanınması güç olabilir. Bu sunumda, çok yüksek lityum düzeylerine rağmen, hafif ve siliik semptomlar gösteren bir olgunun klinik tablosu ve tedavisi literatür ışığında tartışılmaktadır. 37 yaşında bipolar bozukluk hastasının son üç gün içinde gelişen uykusuzluk, bulantı ve ince tremoru vardı ve serum Li düzeyi 5,4 mmol/L bulundu. Hasta, son 10 gündür 1200 mg/gün Li kullanmaktaydı. Forse alkalemi diürez ve destekleyici tedavi ile 24 saatte serum Li düzeyi normal seviyeye indi. Lityum, psikiyatride maksimum alım dozlarına yakın düzeylerde kullanılır. Bazı intoksikasyon olgularında serum düzeyleri normal olabilirken, bazen de akut doz aşımalarında serum düzeyi çok yüksek olabilir. Ancak olgu, normal hücre içi yoğunluk nedeni ile asemptomatik kalabilir. Lityum intoksikasyonunun şiddeti ile en iyi korelasyonu klinik semptomlar gösterirler. Olgumuz, lityum intoksikasyonu tedavisinde kararların, serum lityum düzeylerinden çok klinik parametrelere dayalı olması gerektiğini desteklemektedir.

Anahtar kelimeler: Lityum, akut intoksikasyon, istenmeyen yan etkiler

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Date of receipt:
October 29, 2010

Date of acceptance:
January 18, 2011

INTRODUCTION

Lithium (Li) is one of the most efficacious medications for the treatment of bipolar disorder and prevention of episodes; however, due to its narrow therapeutic window, its toxicity potential is high (1). Mild toxicity develops over a serum Li level of 2.5 mmol/L, severe toxicity develops over 2.5-3.5 mmol/L and life-

threatening toxicity develops over 3.5 mmol/L (2). In acute toxicity, gastrointestinal symptoms such as nausea, vomiting and diarrhea are seen in early period. Various electrocardiogram (ECG) changes can be seen. Neurological symptoms are seen later, due to its slow distribution to central nervous system (3).

Intoxication develops at some stage of treatment process in the most of the patients (70-90%) taking Li

maintenance treatment (4). For this reason, diagnosis of Li toxicity by physicians is important. Due to pharmacokinetic characteristics of lithium, clinical effects of toxicity change according to the type of intoxication. Toxicity symptoms improve rapidly in acute toxicity, but in longterm treatment and chronic toxicity most of the lithium is located intracellular. Thus, toxicity symptoms are more severe and toxicity improves slower in chronic intoxication than acute intoxication (5).

Clinical diagnosis of Li intoxication is difficult because clinical manifestations of toxicity can be different and frequently very subtle. Serum Li levels can be normal in some cases of intoxication (6); however, in acute overdoses serum levels can conversely be extremely high due to late equilibrium of slow diffusion of lithium between intra- and extracellular compartments; patient may remain asymptomatic due to normal intracellular concentration (4). It is widely accepted that clinical symptoms are correlated with severity of intoxication rather than serum Li concentration and it was recommended that clinical parameters should be taken into consideration for the selection of treatment. Although very few in number, there are case reports in the literature showing few symptoms despite the high Li levels. In this report, clinical presentation and treatment of a case showing mild and subtle symptoms instead of very high Li levels is discussed. Informed consent was taken from patient for the report.

CASE

Thirty-seven years old female patient who had a 15 year history of bipolar disorder described seasonal course which most attacks occurred in summer and complete remission between attacks. In her psychiatric history, there was a hospital admission once 5 years ago and valproic acid and olanzapine use after that. In her family history, there was history of bipolar disorder in his uncle. In her own medical history, she described hashish abuse between the ages of 13 and 15, and there were self-mutilative cutting scars in her left forearm belonging to that period.

She was admitted to emergency psychiatry unit due to insomnia, nausea, shivering and restlessness

developed in the last 3 days. She was diagnosed as bipolar disorder, manic exacerbation 10 days ago at our hospital and discharged with treatment order of lithium carbonate 1200 mg/day, haloperidol 20 mg/day and biperidene 4 mg/day. When her admission records were examined, it was seen that her lithium dosage was increased due to serum level of 0.62 mEq/L with 900 mg/day of lithium carbonate for 10 days. When her history was examined deeper, it was learned that polyuria, polydipsia and fatigue developed recently. Her Li serum level was detected 5.4 mEq/L in emergency department which was re-tested twice more.

Her physical examination and vital signs were within normal limits. Her ECG showed sinus rhythm and was within normal limits. In neurological examination, she was alert and fully oriented and there were no pathological findings except a fine tremor. In her psychiatric examination, psychomotor activity was mildly increased, mood was dysphoric and irritable, and her speech amount was increased; there were no psychotic signs and signs of cognitive disorder and her insight was partially preserved. It could not be clarified whether she has taken her medication overdose voluntarily or accidentally during 10 days after her discharge. In her initial laboratory examination, there was leucocytosis (WBC count=14,800 cells/mm³), anemia (RBC count=3,760,000/mm³; Hct=%33.9), hypoproteinemia (serum albumin=3.3 g/dL; total protein=6.1 g/dL), elevated AST and CK levels (AST=52 IU/L; CK=657 IU/L), hypocalcemia (serum calcium level=7.8 mg/dL), borderline sodium level (136 mmol/L), low urea, creatine clearance, uric acid and urine density (urea=12 mg/dL; creatine clearance=63.56 mL/min; uric acid=2.9 mg/dL; urine density=1005). Patient was transferred to emergency medical department and intoxication treatment was administered in intensive care unit.

Saline infusion was started and patient was treated with forced diuresis (4 ampoules of sodium bicarbonate in 4000 cc. saline) in her first day of admission and her sodium level elevated to 143 mmol/L and her urine density to 1020. Patient was transferred to psychiatry department after her Li level was dropped from 5.4 to 0.003 mEq/L.

Table 1: Clinical Characteristics of Lithium Toxicity (4)

	Neurological	Gastrointestinal	Cardiovascular	Renal
Mild	Fine tremor, apathy, fatigue, muscle weakness, hyperreflexia	Nausea, vomiting, diarrhea	T wave variations, intraventricular transmission defects	-
Moderate	Coarse tremor, dysarthria, tinnitus, ataxia, hypertonia, myoclonus	Nausea, vomiting, diarrhea	T wave variations, intraventricular transmission defects	-
Severe	Stupor, epileptic seizure, coma, fasciculations, spasticity, rigidity, coreo-atetosis, paresis, paralysis	Nausea, vomiting, diarrhea	Cardiovascular collapse, ventricular dysrhythmias	Renal failure

DISCUSSION

Li is used in doses close to its maximal intake levels in psychiatry. Its therapeutic window between effective and toxic doses and adverse effects are frequently seen even in therapeutic dose range. Physical tolerance varies between individuals. Most frequent adverse effects of Li treatment are gastrointestinal disorders, edema and tremor (7). It was reported that hand tremor can be a potential indication of overdose (8). Main target organ of Li toxicity is central nervous system.

When serum Li concentration was 5.4 mEq/L, there were no cardiovascular and renal symptoms in our patient. There were only very mild gastrointestinal and neurological symptoms (fine tremor, nausea and irritability) (Table 1).

In the literature, there are two cases reported for acute overdose similar to our patient whom no symptoms were observed even in higher serum Li levels. In the first case, 16 hours after suicide attempt with 45.000 mg (150 caps) Li, in serum Li level of 8.64 mEq/L, no symptom was seen except mild nausea (9). In the second case, 13 hours after acute intoxication with 22.500 mg (50 caps of slow release 450 mg) Li, neurotoxicity and nephrotoxicity could not be detected with 10.6 mEq/L serum Li level and patient was fully recovered by conservative treatment (10).

Cases with cardiac complications and severe neurotoxicity which may also cause sequelae were frequently reported in the literature especially in chronic intoxications and with serum Li levels close to our case (11-14). There are cases in whom various complications were reported with lower serum Li levels compared to our case. For serum Li levels, following complications were reported:

cardiac complication occurring at 1.2 mEq/L (15), coreiform disorder occurring at 0.94 mEq/L and disappearing when level goes below 0.72 mEq/L (16), neurotoxicity at 1.8 mEq/L (17), severe neurological symptoms, status epilepticus and death at 2.86 mEq/L (12).

In lithium overdose, orogastric irrigation is inappropriate; active coal is contraindicated (3). Renal function impairment which is responsive to fluid replacement can be seen in many cases (18). For this reason, restoration of intravascular volume should be focused before all. Renal perfusion, glomerular filtration rate and lithium excretion increase by saline infusion. Urinary output should be monitored and electrolyte imbalance should be corrected. Forced diuresis with loop diuretics, osmotic agents, carbonic anhydrase inhibitors and phosphodiesterase inhibitors should be avoided. Sodium bicarbonate use for urinary alkalization is not recommended because it does not provide additional elimination compared to volume expansion by sodium chloride and may cause hyokalemia, alkalemia and fluid overload. However, our case was closely followed-up for electrolytes, alkalemia and fluid overload, and forced alkaline diuresis was administered and Li levels were reduced rapidly.

There is not a consensus of using advanced elimination techniques and their timing in Li intoxication (5,19,20). Although Li seems to be ideal for hemodialysis, serum concentrations are not always correlated with toxicity due to its toxicokinetic profile (1,3,5). In addition to the clinical presentation, hemodialysis is recommended when Li concentration is >4.0 mEq/L in any type of lithium intoxication or when >2.5 mEq/L in chronic toxicity (3). Peritoneal dialysis should not be performed. In our case, hemodialysis could have been performed because serum Li levels were too high. However,

infusion treatment and general supportive measures were adequate due to mild clinical signs. Hemodialysis or another alternative extracorporeal technique is recommended for three groups of patients: 1) Patients with severe neurotoxicity signs and symptoms, 2) Patients with signs and symptoms of Li toxicity and renal failure, and 3) Patients with mild or no toxicity but intolerable to sodium replacement treatment (i.e., congestive heart failure, hepatic failure, pancreatitis or sepsis). Our case does not belong to any of these groups.



CONCLUSION

Acute Li intoxication is better tolerated than chronic intoxication, and possibility of neurological signs and

permanent sequelae is lower (14,21). Although there are high serum levels in acute Li intoxication cases, target tissues are relatively preserved. For this reason, less symptoms can be observed, serum Li levels do not reflect levels in tissues and correlation between toxicity and Li levels is poor. In the treatment of acute Li intoxication, symptoms should be taken into consideration rather than serum levels. Clinician should determine the severity of intoxication by history taking and serial follow-up of Li levels. Severe neurological morbidity should be prevented or treated and mortality should be prevented by rapid diagnosis, fluid loading and total intestinal irrigation when needed (22). Conservative approach should be the rule as in our case.

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