

# Acute Lithium Intoxication and Factors Contributing to its Morbidity: a 10-Year Review

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## ABSTRACT

**Background:** Lithium has been commonly used for the treatment of several mood disorders particularly bipolar disorder in the last 60 years. This study aimed to analyze patients with lithium intoxication referred to Loghman- Hakim teaching hospital.

**Methods:** This is a cross sectional study that has been done on 108 patients with lithium intoxication during 2001 to 2010. Necessary data were collected by checklists and then analyzed by statistical methods in SPSS version 20.

**Results:** 39.8% of patients were male and most of them were in age group 20-40 years (47.2%). The rate of lithium use in 66.7% of patients was lower than 20 grams and the level of lithium in blood was 1 mEq/lit in 44.4% of patients. The rate of recovery has been significantly relation with BUN, creatinin, Intubation, pCO<sub>2</sub> and pH. There was a significant relation between hospitalized with pH, pCO<sub>2</sub>, Na, absorbent materials, intubation and bicarbonate.

**Conclusion:** Results showed that we should note to the rate and time of lithium used and also severity of signs in management and treatment of patients with the lithium toxicity.

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► *Implication for health policy/practice/research/medical education:* Acute Lithium Intoxication and Factors Contributing to its Morbidity

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## 1. Introduction:

The use of lithium is recognized in the treatment of acute manic phases as well as in the prevention of recurrent manic or depressive episodes in bipolar disorder (1). Use of lithium in case of long-term

pharmacotherapy results in the appearance of cases of lithium toxicity (2-4).

Therapeutic index of lithium is narrow (0.6 to 1.2 mEq/L) and toxic threshold is around 1.6 mmol/L. According to Sheehan (5), mortality due to acute lithium intoxication has been reported 15% (6).

Clinical features of lithium acute intoxication are mostly neurological, and range from drowsiness, slight tremor, headache, apathy with slurred speech, muscle tremors. In most aspects there

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appears serious coma, diffuse muscle twitching and convulsions. Associate digestive disorders such as nausea and vomiting and diarrhea may occur. Cardiac manifestations such as supraventricular arrhythmia are not common, and mostly isolated electrocardiographic changes (QT prolongation, changes in T wave) are reported (7). Kidney related events are not common during acute poisoning by lithium salts, and are often observed during chronic treatment, manifested by nephrogenic diabetes insipidus with polyuria, which may promote dehydration (8).

Toxic manifestations are often reported in patients receiving long-term high doses of lithium: plasma half-life of Lithium can last 12-58 hours in the absence of appropriate clinical management or in patients under long term (more than a year) treatment by the lithium (9). Prolonged treatment with carbonate lithium leads to intracellular accumulation of lithium which can explain the increased half-life lithium plasma level (10). This is independent of the dosage which in the sustained-release forms, delay intestinal absorption about 2-8 hours and the peak urinary excretion 8-24 hours. Other factors, such as renal failure inhibitors may be involved in the accumulation of lithium (11).

In the present study, we aimed to determine the predictive factors on morbidity in patients with lithium intoxication referred to Loghman teaching hospital from 2001 to 2010.

## 2. Materials and Methods:

This is a retrospective, cross sectional study that has been done on 108 patients with lithium intoxication from 2001 to 2010 in Loghman Hakim Hospital. Demographic data (age and gender) and other information, including vital signs at admission time, lithium plasma levels, electrocardiography findings, blood urea, sodium and potassium concentrations, neurologic findings, respiration condition and levels of consciousness, treatments and outcome was registered by a checklists. This study is approved by the medical ethic committee of Shahid Beheshti University of Medical

Sciences. Collected data analyzed by descriptive and analytical statistical methods in SPSS 20.  $P < 0.05$  set as a significant.

## 3. Results:

The demographic and clinical data of the patients are illustrated in Table 1. A total of 108 patients were analyzed that 39.8% of them were male and 60.2% were female. Of all, 47.2% were in an age group 20–40 year old. 59.3% of patients were admitted to hospital in less than six hours after lithium ingestion, while 13.9% were admitted between 6 to 12 hours after ingestion, and 18.5% were taken to hospital more than 12 hours. The amount of taken lithium was reported under 20 grams (gr) in 66.7% of patients, between 20-40 grams in 10.2%, and more than 40 grams in 4.6%. 26.9% of patients had pure lithium toxicity; however 70.4% had taken other drugs besides lithium. 5.6% of patients noted a previous history of seizures, 60.2% had at least a psychiatric disorder, 36.1% had a history of previous suicide attempt, and 4.6% had illicit drug addiction.

All patients with pure lithium intoxication were successfully recovered, but in 3.9% of patients who had taken other drugs rather than lithium, complete recovery was not reported, which shows a significant difference ( $P = 0.001$ ).

93.5% of patients were treated with activated charcoal and sorbitol and 1.9%, were treated with polyethylene glycol. 4 (7.3%) of patients were used as adsorbent. 13% of patients were hospitalized in intensive care unit, and 78.1% were hospitalized in wards. Lithium level in blood was measured  $< 1$  in 44.4% of patients.

There was a strong relationship between GCS and recovery. There was no recovery in two patients with a GCS of 15 (2%), but 50% of patients who had a GCS less than 15 ( $n = 3$ ) did not experience recovery ( $P = 0.001$ ).

Furthermore, we found a significant relation between renal function tests (BUN and creatinine) and recovery. Complete recovery was reported in 100% of patients with BUN  $< 8$ , but the recovery rate in patients with BUN levels among 8-25 and  $> 25$  was 7.16%

and 1.2 consecutively. Moreover, 1% of activated charcoal and sorbitol, 89.1% were

**Table 1:** The mean of vital signs in patients by from of pill

Gender	Male=43 (39.8%) Female=65 (60.2%)
Age	<20 years 36 (33.3%) 20-40=51 (47.2%) >40 (19.4%)
Admission to hospital (after intoxication )	<6 hrs=64 (59.3%) 6-12 hrs=5 (13.9%) >12 hrs=20 (18.5%) Missing data =9 (8.5%)
Lithium amount taken	<20 gr=72 (66.7%) 20-40 gr=11 (10.2%) >40 gr= 5 (4.6%) Missing data=20 (18.5%)
Drugs used by the	Lithium only=29 (26.9%) Lithium+other drugs=76 (70.4%)
GCS	GCS15=102 (94.4%) GCS<15=5 (5.6%)
Pupil size	Normal =105 (97.2%) Myosis=2 (1.9%) Decreased light reflex=1 (0.9%)
Clinical management method	Active charcoal+Sorbitol=101 (93.5%) Polyethylene glycol=2 (1.9%) Conservative treatment=4 (3.7%)
ICU hospitalization	Yes=94 (87%) No=14 (13%)
Amount of Lithium ingestion	< 1 gr=48 (44.4%) 1-2 gr=26 (24.1%) 3 gr=7 (6.5%) 4 gr=2 (1.9%) 5gr=2 (1.9%) Seizures=0
Neurologic manifestation	Nystagmus=0 Tremor=4 (3.7%) Increased deep tendon reflexes=1 (0.9%) Decreased deep tendon reflexes=3 (2.8%)

patients with creatinine clearance between 0.5 up to 1.7 showed symptoms of clinical progress, while recovery was not observed in 44.4% of the group with Cr >1.7 ( $P<0.001$ ). 10 patients (10.3%) were intubated, among them 3 (33.3%) patient did not recover, whereas in non-intubated patients, 2 (2.1%) of them did not recover, which is statistically significant ( $P<0.001$ ). Furthermore, the length of hospitalization in intubated patients was more than non-intubated ones ( $P=0.01$ ).

The length of hospitalization was also associated with the use of absorbent material and polyethylene glycol ( $P=0.001$ ). Because of 101 patients who were treated with

hospitalized for less than 2 days, and in patients for whom polyethylene glycol was utilized, 50% had hospital stay length for more than 2 days.

Patients' length of stay was in relation with the admission time blood gas (PH and HCO<sub>3</sub>) as well. PH between 7.35-7.45 was reported in 95.7% of patients. 4 patients had hospitalization length >7 days, of which 75% had normal PH and 25% had acidosis ( $P=0.009$ ).

We also detected a significant relation between blood PH and HCO<sub>3</sub> and duration of ICU stay. Eight patients had one day ICU stay, among which, one had blood pH <7.35, but in the case of two other patients with

ICU stay > 1 day, blood pH was not normal

**Table 2:** Vital signs and lab tests at admission time

Vital signs		
Blood pressure (mmHg)		<120/80=87 (80.6%)
		120/80-140/90=7 (6.5%)
		>140/90=14 (12.9%)
Heart rate (pulse/min)		<60=3 (2.8%)
		60-100=102 (94.4%)
		>100=3 (2.8%)
Respiration rate (per minute)		<14=1 (0.9%)
		14-20=105 (97.2%)
		>20=2 (1.9%)
Lab tests		
WBC		<4*10 <sup>3</sup> =1 (0.9%)
		4-10*10 <sup>3</sup> =80 (74.1%)
		>10*10 <sup>3</sup> =26 (24.1%)
Na		<135= 3 (2.8%)
		135-145=99 (91.7%)
		>145=5 (4.6%)
K		<3.5=2 (1.9%)
		3.5-5.5=104 (96.3%)
		>5.5=1 (0.9%)
BUN		<8=2 (1.9%)
		8-25=81 (75%)
		>25=24 (22.2%)
Cr		0.5-1.7=98 (90.7%)
		>1.7=9 (8.3%)
PH		<7.35=6 (5.6%)
		7.35-7.45=100 (90.7%)
		>7.45=1 (0.9%)
HCO <sub>3</sub>		<24=7 (6.5%)
		24=90 (83.3%)
		>24=10 (9.3%)
PCO <sub>2</sub>		<35=3 (2.8%)
		35-45=101 (93.5%)
		>45=3 (2.8%)
PaO <sub>2</sub>		<80=1 (0.9%)
		80-105=106 (98.1%)

(P=0.03). Also, in all 8 patients who were hospitalized for 1 day in the ICU, HCO<sub>3</sub> was equal to 24 but in two patients who had ICU stay >1 day, HCO<sub>3</sub> was reported <24 (P=0.02).

#### 4. Discussion:

Since the 1950s, lithium carbonate has been used in the treatment of bipolar depression (4), sustained release forms appeared in 1994 on the market and provided stability with following lithium with a single dose daily. However, this practice exposes advantage to patients with prolonged treatment or involuntary intoxication effects. In such cases, treatment should be consisted of two successive sessions of hemodialysis due to rebound of the lithium level. Severe

neurological clinical manifestations may occur after the first dialysis session. Dehydration remains a very common risk factor in such patients (12). Certain coincidental drugs are known to be related to dehydration: diuretics, non-steroid anti-inflammatory drugs, tetracycline, cyclosporine, angiotensin converting enzyme (8). Besides, febrile conditions associated with neuroleptic malignant syndrome, surgery or infections, a secondary fluid and electrolyte disorder with renal failure or dehydration are risk factors for poisoning (5, 13).

Duration of intoxication before admission to hospital and individual tolerance are also contributory (12). According to one study (6), hyperthermia plays a major role in facilitating the intrinsic neurotoxicity of lithium by its ability to weaken the cell membranes. It may also induce a concept of lithium tolerance variable over time (14). It is important to consider risk factors to prevent poisoning.

Lithium erythrocyte concentration may be a more accurate measurement of the lithium concentration in the brain (5). In case of severe intoxication where lithium levels greater than 3.5 mmol/L, or when the patient's condition is unstable regardless of serum lithium levels, hemodialysis remains the treatment of choice (8).

In a prospective study (15) selected 99 schizophrenic patients older than 30 years under a national health study, with regular follow-up visits. After correction of cardiovascular disease, body mass index (BMI), blood pressure, cholesterol, HDL, exercise, smoking, alcohol, unnatural death and comorbid somatic diseases total mortality increased to 2.25 fold (95% CI 1.46 - 4.30), which increased with the number of neuroleptics treatments used. Causes of increased mortality were related to sudden arrhythmias (Torsades de Pointes), due to prolongation of the QT (ULN 440 ms, TdP risk from 500 ms) (16). There are also cases of sudden death without prolonged QT interval. Overall, mortality rate from suicide in people with schizophrenia diagnosis has been reported between 4% and 13% and on average about 10% (17).

After the first psychotic episode suicide the leading cause of death in the first year is particularly common (18). Another survey found a 37 fold increase, but overall 1.2% rate of suicide in schizophrenic patients diagnosed in the first 3.5 years after the first episode in patients who discontinued antipsychotics. 38% of patients attempted suicide within the first month after tapering the neuroleptics (19). As any other drugs intoxication with lithium is not uncommon. In these cases, appropriate knowledge of lithium intoxication, risk factors and causes, facilitate rapid identification and more effective recovery, which will eliminate the possibility of sequels.

In our study, we found a significant relation between Glasgow Coma scale (GCS) and recovery rate in patients; therefore special attention should be paid to this item at the first visit by the clinician. Moreover, a detailed history should be taken from the patients, while our results showed less recovery in patients with several drugs intoxication. In our study, the recovery rate in patients with impaired renal function tests (BUN and creatinine) was significantly less than the patients with normal BUN and creatinine; this reminds us to consider serial laboratory tests.

### 5. Conclusion:

With regard to the results of study, the clinician should pay attention to patient's medical history (lithium daily dose, time of consumption, other drugs and simultaneous illness) and other key points such as baseline biochemical investigation and blood lithium level, as well as clues found in physical examination. Also the measurement of serum lithium concentration is not sufficient for prediction of lithium toxicity rate and patients prognosis. One of the limitations of our study was the small number of the studied patients in comparison to other studies, and better results could be attained from the study with higher number of selected samples.

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