The Clinical Manifestations of Lithium Intoxication

Eyal Meltzer MD and Shmuel Steinlauf MD

Department of Internal Medicine E, Tel Aviv Sourasky Medical Center, Tel Aviv, and Sackler Faculty of Medicine, Tel Aviv university, Ramat Aviv, Israel

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Abstract

Background: Lithium has been a part of the psychiatric pharmacopoeia for more than half a century. Its efficacy is marred by a narrow therapeutic index and significant toxicity.

Objectives: To increase physicians’ awareness of the various manifestations of lithium intoxication.

Methods: We reviewed the clinical data of cases of lithium poisoning occurring in a municipal hospital during a 10 year period.

Results: Eight patient records were located. The mortality rate was 12.5%. All patients were women and the mean age was 66.4 years. The most common symptoms were neuropsychologic. One illustrative case is described in detail with lithium serum levels showing the usual two-phase decline.

Conclusions: Lithium poisoning can present in many forms. Increased physician awareness and the early use of effective treatment, mainly hemodialysis, will prevent mortality and protracted morbidity associated with this condition.

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Lithium has been used in medicine since the 1860s. Since its introduction by Cade 50 years ago [1], it has proven to be an effective thymoleptic drug, reducing suicide rates and mortality in patients with affective disorders [2-4]. Its main disadvantage is a narrow therapeutic window. Lithium toxicity can cause death and severe morbidity, and may have renal, gastrointestinal, endocrine and predominantly neurologic manifestations [5-8].

This report presents details of an illustrative case of lithium poisoning, followed by a summary of case records of lithium poisoning found in a municipal hospital during a 10 year period.

Methods

We searched the hospital archive using ICD9 codes for cases of lithium poisoning that had occurred during a 10 year period. Medical records were reviewed and epidemiologic and clinical data extracted. We present the medical records of the first case, referred to as the index case.

Results

Index case

The patient was a 55 year old woman, generally healthy apart from a long-standing bipolar affective disorder. Her medications included lithium, haloperidol and fluoxetine. She was referred to the emergency room because of agitation, confusion and incontinence. Li level was 4.5 mEq/L. The patient was initially confused, and during her stay in the emergency room delirium, tremor and impaired speech developed. Saline and furosemide diuresis was initiated and the patient was admitted to a medical intensive care unit. On the following day she developed generalized and focal seizures and lapsed into a coma vigil-like state, with generalized rigidity and frontal signs. The patient was polyuric. Notable laboratory findings included neutrophil leukocytosis, azotemia, hypernatremia, glycosuria without hyperglycemia, and mildly elevated liver and muscle enzyme levels. Thyroid and parathyroid function was normal. On the fourth day the patient began to communicate with head nods. Her speech was very slow and slurred. Hypomimia, rigidity, coarse limb tremor and bradyphrenia resolved slowly during the next 3 weeks, while anxiety and depression increased simultaneously. The patient was discharged for further in-patient psychiatric care after 25 days. At that time the only finding was slurred speech.

The Li serum level showed a rapid initial decline during the first day, followed by a further slow decline well into the second week of her stay [Figure 1]. Li was still excreted in the urine after 13 days.

Review of lithium poisoning cases

During a 10 year period nine cases of lithium poisoning were reported. The medical records of eight of these patients were available for review. All patients were females with a mean age of 66.4 years (range 55–78). The mean hospital stay was 8.8 days (range 3–25). The mean Li serum level was 2.63 (range 1.61–4.5) and the mortality rate 12.5%.

Figure 1: Lithium serum levels in an index patient

Li = lithium
Table 1 summarizes the various manifestations of Li poisoning and their incidence. In only two of our cases was there a history of acute Li overdose, one of which was a suicide attempt. The other patients were on chronic treatment with Li. Two were referred from a long-term care psychiatric facility. Another two were treated concomitantly with angiotensin-converting enzyme inhibitors, and another with thiazide diuretics.

**Discussion**

Lithium poisoning is a serious and sometimes deadly condition. Obviously, this case series, being limited to patients hospitalized because of lithium poisoning, represents the more severe end of the clinical spectrum of this condition.

Therapeutic Li serum levels range between 0.8 and 1.2 mEq/l. There is some correlation between Li serum levels and the severity of side effects. Some of the symptoms present during intoxication, such as urine concentration abnormality, abnormal thyroid function tests, tremor, and gastrointestinal disturbance. These symptoms occur in a significant minority of patients who are treated chronically and whose Li levels are within the therapeutic range. Therefore, the distinction between mild toxicity and side effects is blurred [7].

The patients were a mixed population of acute and chronic toxicity, and in two of them toxicity occurred while they were hospitalized in a psychiatric hospital. This is not unusual. In a recent series more than half the cases of Li toxicity occurred after hospitalization [8].

A mortality rate of 12.5% is in accordance with previous reports [9]. All patients had central nervous system manifestations of Li poisoning, which were also prevalent in previous reports [6]. CNS-related symptoms are protein [8], but tremor, ataxia and dysarthria are common [8].

Vomiting and diarrhea are common side effects of Li intoxication [6]. It is noteworthy that our most severe cases, the index case and the one fatality did not have gastrointestinal related symptoms. Lithium-induced vomiting and diarrhea may have a role in limiting Li absorption and thus disease severity.

Furthermore, our patients, all of whom were postmenopausal, presented with two of the typical risk factors for Li toxicity – advanced age and female gender.

Of clear importance are conditions that decrease renal clearance of Li. Following filtration, 80% of Li is reabsorbed in the proximal tubule, along with water and sodium. All conditions that decrease the glomerular filtration rate or increase proximal reabsorption may induce Li toxicity. These include dehydration, sodium restriction, and medications, including thiazide diuretics, non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors. One should also be aware of over-the-counter and non-conventional medications. One case of Li poisoning reported later was associated with the use of a herbal diuretic formulation [10].

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<th>Pt. #</th>
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Table 1. Patients’ clinical findings

The index case provides insight into the pharmacokinetics of lithium. Li ions are rapidly absorbed from the gastrointestinal tract and plasma lithium peaks are reached 2–6 hours after Li administration [11–13]. From the extracellular compartment Li enters the intracellular compartment, leading to an initial decline in serum Li levels that can be mistaken for response to therapy. Elimination of intracellular Li is slow and can take several days. It may be even more prolonged in patients on chronic therapy [14]. It is obvious therefore that for therapy for Li poisoning to be effective, it should be employed early to exert a rapid clearance of Li [15].

Several reports have shown that hemodialysis – both intermittent and continuous – is effective [16,17]. Li clearances of 48–62 ml/min can be reached, as compared to a maximal renal clearance of approximately 10–20 ml/min [17]. Dialyzer Li removal is consistently reported as being five to sixfold greater than that of renal Li [17,18]. Although concern has been raised over rebound Li levels after dialysis [19,20], this modality should be considered the treatment of choice for severe Li poisoning.

As evident from our index case, saline diuresis was found to be an ineffective method for Li elimination [21]. An effective oral treatment adjunct is the administration of sodium polystyrene sulphate, which can prevent Li absorption when used early after ingestion [22–24]. Sodium polystyrene sulfate has been shown in an animal model to increase Li elimination even when Li was given parenterally [25]. Even when used late after acute Li overdose it has been reported to be beneficial, and it may well have a place in the treatment of chronic Li overdose and poisoning caused by sustained-release tablets.

**Conclusions**

Li poisoning can present in many forms: from an illness that might be mistaken for gastroenteritis to a catastrophic multi-system and especially neurologic dysfunction. The best approach is certainly the use of preventive measures. Avoidance of dehydration, sodium depletion and the use of NSAIDS, diuretics and ACE inhibitors can
prevent cases of Li toxicity. Only increased physician awareness and the early use of effective treatment, namely dialysis, will prevent the mortality and protracted morbidity associated with this condition.

References


Correspondence: Dr E. Meltzer, Dept. of Internal Medicine E, Tel Aviv Sourasky Medical Center. 6 Weizmann St., Tel Aviv 64239, Israel. Phone: (972-3) 697-3705. Email: meltzer@matav.net.il

Capsule

The hormone relaxin

The hormone relaxin has long been recognized as important to mammalian reproductive processes, and the development of therapeutics to treat preterm labor disorders and delivery problems has been stifled by the elusiveness of its cognate receptor. Hsu et al. have identified a G protein-coupled receptor that mediates the effects of relaxin. This is somewhat surprising because a structurally similar hormone, insulin, signals through a receptor-type tyrosine kinase.

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Capsule

Steps toward mapping the human vasculature by phase display

The molecular diversity of receptors in human blood vessels remains largely unexplored. Arap and associates developed a selection method in which peptides that home to specific vascular beds are identified after administration of a peptide library. The authors report the first in vivo screening of a peptide library in a patient. They surveyed 47,160 motifs that localized to different organs. This large-scale screening indicates that the tissue distribution of circulating peptides is non-random. High throughput analysis of the motifs revealed similarities to ligands for differentially expressed cell-surface proteins, and a candidate ligand-receptor pair was validated. These data represent a step toward the construction of a molecular map of human vasculature and may have broad implications for the development of targeted therapies.

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