

Lithium Overdose and Delayed Severe Neurotoxicity – Timing for Renal Replacement Therapy and Restarting of Lithium

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Summary

This is a case report of a gentleman in his sixties who presented to an English hospital following a significant Lithium overdose. He was monitored for 24 hours, and then renal replacement therapy was initiated after assessment by the renal team. As soon as the Lithium level returned to normal therapeutic levels (from 4.7mEq/L to 0.67mEq/L), Lithium was restarted by the medical team. At this point, the patient developed new slurred speech, and later catatonia. In this case report, we discuss the factors that could determine which patients are at risk of neurotoxicity following Lithium overdose, and the appropriate decision regarding when and how to consider initiation of renal replacement therapy and restarting of Lithium.

Background

Lithium in clinical use

Lithium is a naturally-occurring salt, or alkali element, which was discovered serendipitously to relieve mood disorder and was introduced into therapeutic clinical practice in the middle of the 20th century [1]. It is now widely used as a first line medication for maintenance therapy for bipolar affective disorder as recommended by the National Institute for Health and Care Excellence (NICE) and well-known Psychiatry prescribing guidelines such as the Maudsley Prescribing Guidelines [2, 3]. Lithium also is used in the clinical management of other medical conditions such as recurrent depressive disorder, cluster headaches, migraines and impulsive behaviour [3, 4]. One of the major drawbacks for the use of Lithium is its narrow therapeutic index resulting in toxicity especially renal. This toxicity could be the outcome of an accidental or intentional overdose, or intoxication due to reduced renal clearance (as 95% of ingested Lithium is cleared by the kidney).

Lithium and neurotoxicity – clinical features, risks factors, and pathophysiology

Despite over 60 years of medical experience with Lithium, neurotoxicity resulting from Lithium therapy remains poorly understood [5]. Neurotoxicity is a diverse spectrum of neuropsychiatric symptoms that rarely occurs directly related to brain trauma from use of lithium. These symptoms as described in previous case reports include confusion, mental slowing, dysarthria, mood changes, memory and fronto-executive dysfunction, seizures and stupor [6-8]. These effects occur typically secondary to serum intoxication, but neurotoxicity has also been reported infrequently at therapeutic levels [7].

Here we describe a case of severe Lithium overdose, where neurotoxicity symptoms developed in a delayed presentation. We also discuss the potential relevance of the timing for renal replacement therapy and restarting of Lithium even when Lithium levels are considered below the established toxic threshold.

Case presentation:

A gentleman in his 60s with a previous history of recurrent depressive disorder was hospitalised for a significant Lithium overdose. Prior to admission, he was taking Lithium Carbonate 800mg ON, Clomipramine 75mg ON and Quetiapine 200mg ON under the supervision of his General Practitioner. He was last known to community mental health services seven years previously and had 3 prior informal admissions, the most recent for severe depression with self-neglect in 2003. The patient also self-reported an overdose of Zopiclone a few years before this admission, but there was no collateral history of this. In the months leading up to the Lithium overdose, he had been diagnosed with a rare skin carcinoma on his leg, and had undergone radical surgery which he described as particularly distressing. He was socially isolated following a relationship breakdown approximately one year before admission.

This gentleman self-administered 50 x 400mg Lithium Carbonate alongside 1 pint of beer, and had made preparations for death. 12 hours later, he called an ambulance due to dizziness, profuse vomiting, diarrhoea, and abdominal pain. He reported the overdose to the paramedics and the admitting medical staff. At the time of presentation, the gentleman was found to be suffering from a relapse of a severe depressive episode with biological (poor sleep and appetite) and psychological symptoms (hopelessness, helplessness, ongoing suicidal ideation), and social withdrawal. There was no history of an alcohol misuse disorder.

Investigations:

On admission, this gentleman was clinically dehydrated and appropriate neurological examination demonstrated cerebellar ataxia and past pointing, but no other abnormality. Investigations confirmed that creatinine was raised from baseline (108µmol/L versus 75 µmol/L baseline, normal range 64-111µmol/L), and venous blood gas on admission showed pH 7.41 (7.35-7.45), bicarbonate 28.1mmol/L (22-26), base excess 2.8mmol/L (-2 to +2), lactate 1.5mmol/L (0.6-1.4). A serum Lithium level (12 hours after overdose) was 4.7mEq/L (normal therapeutic range 0.4-1.0mEq/L). He had a prolonged QTc of 490ms and right bundle branch block (RBBB) on ECG. All other investigations were normal.

Treatment:

24 hours after presentation, the admitting medical team started haemofiltration, of which he underwent 3 episodes. All psychotropic medications were withheld. Serum lithium level was reduced to 2.1mEq/L after two episodes of haemofiltration, and further to 0.88mEq/L after the third haemofiltration episode.

Outcome and follow-up:

When the serum Lithium level was 0.67mEq/L and six days after the overdose, the medical team restarted Lithium at 400mg ON. Within 24 hours, the patient developed bilateral tremor, dysarthria, and dystonia, all of which had been absent on admission. On consultation with the Liaison Psychiatry team, Lithium treatment was immediately re-stopped. A repeat random serum Lithium level was confirmed at this stage to be below the therapeutic window (0.24mEq/L). Subsequent CT head and MRI brain showed no acute abnormality. A repeat ECG demonstrated a QTC of 442ms and no RBBB. The patient remained low in mood with suicidal thoughts, and therefore quetiapine 50mg ON was restarted and mirtazapine 15mg ON initiated for a relapse of a depressive episode. Neurology opinion was not available on-site, and so this was organised as an outpatient for the new neurological symptoms as they did not appear progressive.

Three weeks after acute medical admission, the patient was transferred to psychiatric hospital as an informal patient. Shortly after transfer, he deteriorated again and showed signs of catatonic stupor. He was therefore detained under section 3 of the MHA and underwent 3 sessions of ECT.

Discussion:

Lithium and neurotoxicity – risks factors, and pathophysiology

Oakley and colleagues performed a retrospective analysis of 97 case records of Lithium toxicity over a 13-year period at one regional centre in Australia. They found that neurotoxicity appeared to be at least partially dose-related, with severe symptoms more likely to occur at greater Lithium serum levels (2.3 vs. 1.6 mmol/L, $p = 0.02$) [5]. The greatest risk of neurotoxicity was for those patients on chronic lithium where either insidious toxicity or acute toxicity occurred: patients presenting with chronic poisoning (chronic or acute-on-chronic) were at greater risk of severe neurotoxicity than those presenting after an isolated acute lithium overdose (odds ratio 136, 95% confidence intervals (CI) 23-1300) [5]. They also identified the key risk factors for increasing the risk of neurotoxicity, which were age over 50 years old, renal disease (nephrogenic diabetes insipidus or renal failure) and any thyroid disease [5]. Therefore, from their findings and our observation, this suggests that the gentleman in his 60s discussed in this case report with an acute-on-chronic severe toxicity (Lithium level of 4.7mEq/L) could be considered at high risk of severe neurotoxicity.

Neurotoxicity may be reversible or irreversible. Cerebellar signs such as ataxia and dysarthria are more likely to be irreversible [9] with one case report also indicating that praxis and visuospatial difficulties can persist after resolution of other cognitive functions [6]. EEG has been reported to show diffuse slowing during acute neurotoxicity [6]. Brain imaging (including MRI) may be reported as normal [6] as in our case, and is not universally completed. For these reasons, and likely due to the acute physical condition of the involved patients, determining the underlying brain region dysfunction caused by Lithium toxicity has been difficult. Bartha and colleagues suggest that the

damage may be widespread: a combined, multifocal functional impairment of subcortical and cortical neural mechanisms in both hemispheres [6]. Post-mortem neuropathological examination in one case report of acute-on-chronic toxicity revealed severe cerebellar atrophy of the internal granule and Purkinje cell layers with Bergmann gliosis, with Alzheimer-type related changes in the thalamus and lentiform nuclei possibly due to terminal uraemia [8].

In this case, “lithium rebound” may also have been a contributory factor to the clinical deterioration seen after stopping of haemodialysis. Lithium rebound is an increase in Lithium serum levels, and potentially recurrence of toxicity symptoms, after the cessation of extracorporeal treatment [10]. Typically, this occurs over the following 6-12 hours, although it may be longer in the situation of delayed absorption preparations or decreased gastrointestinal mobility [10].

How to manage Lithium toxicity and neurotoxicity

The United States Extracorporeal Treatments in Poisoning Workgroup (EXTIP) published recommendations on the use of renal replacement therapy for poisoning in 2015 [10]. The EXTIP workgroup reviewed 166 articles (mostly case reports totalling 418 patients), of which they could extract patient-level data in 228. They concluded that lithium is dialysable and that extracorporeal treatment is recommended in severe lithium poisoning, if kidney function is impaired and the Lithium level is higher than 4.0 mEq/L, or in the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of the Lithium level. Extracorporeal treatment is also suggested if the Lithium level is more than 5.0 mEq/L, significant confusion is present, or the expected time to reduce the Lithium level to less than 1.0 mEq/L is more than 36 hours. Extracorporeal treatment should be continued until clinical improvement is apparent or serum Lithium is below 1.0 mEq/L. Extracorporeal treatments should be continued for a minimum of 6 hours if the serum Lithium is not readily measurable [11]. The UK Poisons Advice Service relays similar advice to UK physicians, although no UK national guidelines relating to Lithium and renal replacement therapy exist.

The US guidelines imply that specific symptoms of neurotoxicity, such as seizures, reduced consciousness or confusion should be managed with renal replacement therapy regardless of the serum Lithium level. They also advise extracorporeal therapy for those with several ingestion or high serum Lithium levels even in the absence of specific symptoms. Additional management of Lithium neurotoxicity appears unclear beyond symptomatic management of delirium, seizures and agitation. Therefore, if we apply these recommendations to our case, it suggests that renal replacement therapy in the case of our patient management was appropriate due to the high Lithium level and initial acute renal failure. However, there is uncertainty regarding the timing of renal replacement therapy (i.e.) should this be performed immediately in A&E or wait until a delay of up to 24 hours after medical admission as this decision could influence dramatically the clinical outcomes.

In situations where an informed clinical decision has been made to restart Lithium as a treatment following toxicity, appropriate timing of this can be guided by pharmacokinetics and serial Lithium serum levels [12].

Learning points / take home messages (5 bullet points)

- Lithium neurotoxicity is a potential complication of Lithium therapy, most typically in patients on chronic Lithium who experience an acute overdose or reduced renal Lithium clearance.
- The understanding of how this neurotoxicity occurs at a brain regional level is uncertain, but involvement of the cerebellum and basal ganglia fits with the clinical picture and putative evidence.
- US guidelines indicate that symptoms of severe neurotoxicity (regardless of the serum Lithium level) or if the Lithium level is greater than 4.0mEq/L with poor renal function (regardless of any neurotoxicity symptoms) merit strong consideration of renal replacement therapy to prevent sequelae.
- Some neurotoxic symptoms will resolve on treatment, but some may be irreversible, particularly cerebellar symptoms.
- There is a definite paucity of data regarding the underlying brain regions involved in Lithium toxicity, and whether any specific management, or the exact timing of renal replacement therapy, can affect the prognosis of neurotoxic symptoms and their resolution.

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