

Lithium Neurotoxicity

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Summary

In spite of the advent of newer antimanic drugs, lithium carbonate remains widely used in the treatment and prevention of manic-depressive illness. However care has to be exercised due to its low therapeutic index. The central nervous system and renal system are predominantly affected in acute lithium intoxication and is potentially lethal. The more common side effect involves the central nervous system. It occurs early and is preventable. We describe three cases of lithium toxicity admitted to Johor Bahru Hospital, with emphasis on its neurological preponderance.

Key Words: Lithium carbonate, Toxic effects, Neurotoxicity

Introduction

Lithium carbonate has been an invaluable drug in psychiatry since its discovered to have antimanic effect. The recommended uses of lithium is, in the treatment of acute mania, prophylaxis of bipolar disorder and augmentation treatment for acute depression in resistant cases. Lithium has been proven to reduce or prevent hospitalization of affected patients. The toxic effects of lithium are well established with multisystem organ involvement. The predominant target organs are the thyroid glands, the kidneys and the central nervous system. Neurological side effects of lithium are the commonest side effects. It occurs early and is preventable. Fatal toxicity has been reported in 15% of patients with severe lithium toxicity¹.

Three cases of lithium toxicity were seen in Hospital Johor Bahru from the end of 1996 until the end of 1997. The clinical presentations of lithium toxicity are elaborated in the case reports below with emphasis on the neurotoxic effects of lithium.

Case 1

CMY, a 44-year old single Chinese lady was diagnosed with bipolar disorder for more than 30 years. In January 1997, she was admitted to the Mental Hospital for aggressive behavior. Her medications were lithium carbonate 500mg bd, chlorpromazine 400mg daily and a depot injection of clopenthixol decanoate 200mg once every four weeks. On admission she was noted to be stiff, bradyphrenic and hypersalivating. Her speech was slurred. She was elated with delusions of grandeur. Physical findings revealed cogwheel rigidity and fine tremors in both hands. A diagnosis of drug-induced Parkinsonism was made. Her antipsychotics were stopped, but she went on to develop dysphagia, worsening dysarthria and marked dystonia. Lithium was eventually stopped when she became drowsy. She was in a stupor by the time she was transferred to the general hospital. Her serum lithium level was 3.3mmol/l. A second serum lithium sample was at a high of 5.48mmol/l. The CPK was normal but liver enzymes were raised (Alkaline phosphatase: 163IU/L; alanine

transaminase: 138IU/L). Other investigations include serum creatinine: 0.19 mmol/l; urea: 13.2mmol/l and a TWBC of $14.6 \times 10^9 /L$

Peritoneal dialysis was instituted 72 hours after admission. She regained consciousness after the 24th cycle of the dialysis when her serum lithium level had dropped to 0.8mmol/L. By the time the dialysis was completed, she was able to make some attempt at communication. She continued to show improvement in her mental state but remained dysarthric and ataxic with persisting extrapyramidal symptoms. CT scan done was normal. She remained at the Mental hospital for another 2 months. At discharge, she continued to have weakness of both lower limbs but was able to ambulate with support.

Case 2

SK was a 45-year-old divorced Indian lady. She was diagnosed with bipolar disorder from the age of 17. Lithium was started in 1990 as a prophylaxis for mania, despite of her poor compliance and poor family support. She had several admissions to the Mental Hospital for relapses of mania. Her last admission in September 1996 was for depression. Lithium was increased to 1200mg daily when she went into a manic swing. She was also on haloperidol, 60mg daily.

In the month of October she developed recurrent diarrhea with vomiting, relieved temporarily with symptomatic treatment. Despite these symptoms, lithium was continued without any monitoring. By early May 1997, she frequently complained of dizziness and weakness. She was thought to be in a depressive phase resulting in the addition of an antidepressant. Serum lithium level was eventually sent when her condition worsened. The lithium level was found to be in a toxic range of 2.65mmol/l. All medication were stopped. A repeat lithium prior to her transfer to the general hospital was 3.16mmol/l urea: 14mmol/L; sodium 124.8mmol/l; potassium: 4.3mmol/l and random blood sugar: 23.7mmol/l.

She was drowsy on admission to the medical unit, but was able to obey simple commands. The ECG showed T wave inversion in V1, V2 and V3 leads. A diagnosis of diabetic ketoacidosis was made. Treatment with hydration and insulin were initiated. No psychiatric consultation was requested. She lapsed into a coma and died on the fourth day of admission. Consent for post-mortem was denied. The preliminary cause of death was septicemia with diabetic ketoacidosis. A mortality conference held with the attending physicians concluded the cause of death as due to lithium toxicity with associated diabetic ketoacidosis.

Case 3

LGS, a 37-year-old Chinese lady, was initially diagnosed to have schizophrenia. She had several admissions to the Mental Hospital, each time for suicidal attempts. On her last admission to the Mental Hospital in 1991 for aggressive behavior, her diagnosis was changed to bipolar disorder. Lithium carbonate was added to stabilize her mood and control her aggression. The dosage of lithium carbonate was increased to 1800 mg daily before her symptoms remitted. She was also on a monthly depot clopenthixol decanoate 200mg and oral haloperidol 30mg daily. Maprotiline, 75mg, an antidepressant was added when she attempted suicide. She improved initially but, developed intermittent episodes of diarrhoea and vomiting. Lithium carbonate was stopped when the level was found to be in the toxic range of 4.42mmol/l.

At admission to the General Hospital, she was drowsy but arousable. She was found to have tremors of the tongue. Within 2 hours of admission her general condition deteriorated. Repeat serum lithium showed a level of 4.93mmol/l. Peritoneal dialysis was commenced immediately. The relevant blood investigations were normal. She remained in a coma following the dialysis despite achieving a normal serum lithium level of 0.69mmol/L. She was pronounced dead from lithium toxicity and septicemia on the tenth day of admission.

Discussion

The nervous system is particularly sensitive to lithium. The nervous system side effects are usually prominent at the initiation of treatment but recede with accommodation. Exaggeration of the subtle changes of neurological and neuromuscular effect provides the first and most reliable clue to the impending toxicity. The agitation and the restlessness of early intoxication are similar to the symptoms of mixed affective state and distinguishing between the two phenomena can be difficult. Early signs of neurotoxicity can occur at levels of 1.3 - 2mmol/L and maybe entirely reversible. Toxicity is known to occur with plasma level within the therapeutic range². Recognition of the signs and symptoms of lithium toxicity is important as the toxic effects are not always reversible and death may ensue.

All three patients showed symptoms of restlessness, agitation and depression prior to the emergence of the frank symptoms of neurotoxicity. In the first patient, the symptoms of restlessness and agitation were assumed to be due to her manic symptoms. The extrapyramidal symptoms that were found on examination were attributed to the effect of the antipsychotic rather than to lithium toxicity. Similarly in the second patient, she was presumed to have gone into a manic swing, which lead to a further increase in the lithium dosage, without first checking her serum lithium level. The third patient illustrated what would likely happen when the signs and symptoms of lithium toxicity are overlooked and appropriate strategies are not taken.

One of the many risk factors that can predispose a person to develop lithium toxicity is the presence of a physical illness associated with vomiting and/or diarrhea³. The patients in the second and third case illustration presented with early symptoms of gastro-intestinal disturbances, that is, diarrhea and vomiting before progressing to develop neurotoxic symptoms. Appropriate steps that should have been taken include checking the serum lithium level and stopping or adjusting the dosage of the lithium carbonate. The

presence of psychotic symptoms and intense anxiety can increase a person's vulnerability to the development of severe neurotoxicity. All the three patients had similar presentation as in an earlier report⁴.

The concomitant use of neuroleptic is a common practice, especially in patient presenting with mania. Neuroleptics particularly phenothiazine and haloperidol have been known to have deleterious interactions with lithium⁵; the former by increasing the intracellular uptake of lithium. Lithium carbonate increases the dopamine blocking effects of the latter. Less reported are the interactions of lithium carbonate and tricyclic antidepressant. All three patients were on high doses of antipsychotic. The first patient is on chlorpromazine and clopenthixol; the second patient on haloperidol and the third patient on a combination of haloperidol, clopenthixol and an anti-depressant drug, maprotiline.

There are factors that need to be considered before lithium can be initiated. The second patient was not a good candidate for lithium therapy as her relapses were due to her poor compliance. Lithium therapy should not have been re-initiated in view of poor family support and poor monitoring of lithium at home. In the third patient, her impulsive behavior is the main problem. An alternative treatment strategy such as behavioral techniques to control her impulsiveness would have been safer. Her frequent mood swings at home and in the ward was mainly secondary to the poor family dynamics. Throughout her hospitalization, family visits were rare and requests by the hospital to take the patient home were largely ignored by her family. Family work should have been initiated during her stay in the hospital, which might be of more help to her than lithium.

Continuous monitoring remains important because of the lithium's low therapeutic/toxicity index. All the 3 cases above illustrated the lack of monitoring of lithium inspite of being in a hospital set-up.

A more significant measure of neurotoxicity is the brain concentration of lithium rather than the serum level. It is uncertain at what point lithium toxicity becomes irreversible. This seems likely to depend on the duration of exposure to toxic lithium levels⁴. Dialysis is the only treatment modality that consistently and effectively increases lithium ion clearance. Prolonged and repeated dialysis is required due to the redistribution of lithium ion from tissues. In spite of this, some patients are left with persistent neurological deficit and a few die. Two of the patients underwent peritoneal dialysis but in spite

of this, the first patient was left with a persistent cerebellar deficit while it was too late to save the third patient. In both cases the serum lithium levels following the dialysis returned to normal.

In conclusion; prevention is the most important principle in managing lithium toxicity and these can simply be averted by educating doctors and patients on the side effects of lithium, the risk factors that can predispose one to the toxic effects of lithium, by familiarizing oneself to the early signs of toxicity and by adjusting the dosage of lithium carbonate accordingly.

References

1. Hansen HE, Amdisen A. Lithium intoxication (Report of 23 cases and a review of 100 cases from the literature). *Q J Med* 1978; 47: 123-44.
2. Bell AJ, Cole A, Eccleston D and Ferrier IN. Lithium neurotoxicity at normal therapeutic levels. *Br J Psychiatry* 1993; 162: 689-92.
3. Lenox RH and Manji HK. Textbook of Psychopharmacology. Schatzberg AF and Nemeroff (ed). American Psychiatric Press Inc. 1995; 303 -49.
4. West and Metzler HL. Paradoxical lithium neurotoxicity: a report of 5 cases and a hypothesis about risks of toxicity. *Am J Psychiatry* 1979; 136(7): 963-66.
5. Simard M; Gumbiner B; Lee A *et al*. Lithium carbonate intoxication: A case report and review of the literature. *Arch Intern Med* 1989; 149: 36-44.