

# A case report of a bipolar disorder patient with severe lithium poisoning possibly induced by interaction between risperidone, telmisartan, fluvoxamine and lithium

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## ABSTRACT

We describe a case of severe lithium poisoning possibly induced by multiple drugs interaction. A 45-year-old man with bipolar disorder was admitted with altered behavior and mental status. He was maintained on lithium for 20 years. Nine months ago, lithium dose was increased and risperidone was added. Telmisartan was prescribed around 25 days ago and he had mild tremor since then. Two days ago, fluvoxamine was initiated and he developed restlessness, agitation, insomnia and confusion after one dose. On admission, fluvoxamine, lithium, telmisartan and risperidone were discontinued. Abnormal findings were temporary ST depression, hyponatremia and high creatine kinase. He had fever since day 2 and was covered for meningoencephalitis and neuroleptic malignant syndrome. On the next day, his was comatose and treated for septic shock. On day 7, result of serum lithium taken on day 3 revealed severe toxicity (3.2 mEq/L). The lithium level was normalized after hemodialysis. He subsequently regained full Glasgow Coma Scale score and his toxicity completely resolved on day 16. Interactions of risperidone and telmisartan with lithium possibly precipitated the lithium toxicity. However, the onset of the toxicity suggested fluvoxamine as the major cause of poisoning. Clinicians should be aware of these potential drug interactions.

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## INTRODUCTION

Lithium salts have been used in the prophylaxis and treatment of depression and bipolar disorder for more than 50 years. Lithium is a naturally occurring alkali metal and monovalent cation chemically similar to Na<sup>+</sup> and K<sup>+</sup>. The exact mechanism by which it stabilizes mood is not known. It is thought to affect the central nervous system (CNS) by altering nerve conduction, cortisol and monoamine metabolism, and increasing serotonin (Timmer and Sands, 1999). Lithium has a narrow therapeutic range of 0.6 to 1.2 mEq/L. Toxicity can occur at concentrations greater than 1.5 mEq/L. Most poisonings are a result of altered kinetics (change in dosing or elimination) in patients taking lithium chronically. Renal dysfunction, sodium depletion, nonsteroidal antiinflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists

(ARB) and thiazide diuretics increase serum lithium concentration by reducing renal excretion. Some drugs, such as selective serotonin reuptake inhibitors (SSRI) induces lithium toxicity without changing renal clearance, presumably by increasing 5-hydroxytryptamine (serotonin) metabolites in the cerebrospinal fluid (CSF) (Gill *et al.*, 2003). Mild to moderate poisoning can cause gastrointestinal symptoms such as nausea, vomiting, diarrhea and dehydration. CNS effects such as nystagmus, tremors, hyperreflexia, cogwheel rigidity, ataxia, agitation, confusion and lethargy are common. Cardiovascular (bradycardia and T-wave abnormalities) and respiratory problem (hypoventilation) may also occur (Gill *et al.*, 2003; Okusa and Crystal, 1994; Timmer and Sands, 1999). Patients with chronic toxicity may manifest severe toxicity despite relatively modestly elevated serum lithium concentrations. These severe toxicity effects include photophobia, dehydration, electrolyte imbalances, thyroid dysfunction, hyperthermia, seizure, coma, rigidity, myoclonus and serotonin syndrome.

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Despite nonspecific T-wave abnormalities, such patient may experience electrocardiogram (ECG) changes such as QT prolongation, bundle branch block, bradycardia and junctional rhythm. Respiratory failure and acute respiratory distress symptoms (ARDS) may rarely develop (Gill *et al.*, 2003; Okusa and Crystal, 1994; Timmer and Sands, 1999). Here we describe a case of severe lithium poisoning possibly induced by interaction between risperidone, telmisartan, fluvoxamine and lithium.

### Case Report

A 45-year-old, 75 kg man with 20 years history of bipolar disorder was admitted to neuromedical ward due to suspected lithium toxicity. He was noticed to have altered behavior and mental status for the past 2 days and decreased oral intake markedly for the past 1 week. Other than that he had vomiting for 1 day and diarrhoea for the past 2 days (2 to 3 times a day).

The patient had been successfully maintained with lithium carbonate tablet for the past 20 years for his bipolar disorder. Nine months ago the dose was increased from 600 mg twice daily to 900 mg twice daily due to worsening of his condition. At the same time risperidone 1 mg daily at night was added to his treatment. Twenty five days prior admission, he was started on telmisartan 40 mg once daily, aspirin 100 mg once daily, clopidogrel 75 mg once daily and lovastatin 20 mg once daily following an angioplasty. He was noted to have mild tremor since then. Patient was also a known case of type II diabetes mellitus and hypertension, taking metformin 1 g twice daily and metoprolol 25 mg twice daily.

Two days before admission, fluvoxamine 50 mg once daily was added to his bipolar disorder treatment after following up at psychiatry clinic. He took 1 dose of fluvoxamine at the night itself and subsequently after the dose he developed restlessness, agitation and difficulty to sleep. He was only able to sleep for 3 to 4 hours after he had taken one tablet of alprazolam 0.5 mg. Subsequently, he discontinued fluvoxamine by himself on the next day. However, he developed confusion and was unable to recognize his family members. Due to the deterioration of his mental status, he was admitted by his family members.

On admission, the patient presented with a Glasgow Coma Scale (GCS) score of 14, blood pressure of 107/54 mmHg, pulse rate of 94/min, temperature of 37.5°C, random blood glucose of 8.3 mmol/L and was dehydrated. The electrocardiographic (ECG) examination revealed temporary ST depression at lead I and II which returned to normal later. A complete blood count showed a slightly low hematocrit of 38%, elevated white blood count of  $11.6 \times 10^3/\mu\text{L}$  and normal platelet count of  $245 \times 10^3/\text{mm}^3$ . The renal profile showed a calculated creatinine clearance of 32.3 mL/min, while serum electrolyte analysis revealed sodium level of 126 mmol/L and potassium level of 4.1 mmol/L. The patient's coagulation values showed a prothrombin time of 12.0 seconds, activated partial thromboplastin time of 19.1 seconds, and international normalized ratio of 1.1. Liver function tests showed normal values for alanine aminotransferase (20 U/L), alkaline phosphatase (158 U/L), lactate dehydrogenase (113 U/L) and

aspartate aminotransferase (24 U/L). Level of creatine kinase (CK) (1033 U/L) was elevated. Lithium, telmisartan and risperidone therapy were stopped on day 1. Computed Tomography (CT) brain scan showed no intracranial bleeding and the repeated scan showed no focal paranchymal lesion. On day 2, the patient developed spiking temperature and was treated as meningoencephalitis with intravenous (IV) ceftriaxone 2 g twice daily and IV acyclovir 500 mg three times daily. He was also covered for neuroleptic malignant syndrome with oral bromocriptine 5 mg three times daily. A blood sample was collected on day 3 to check for the lithium concentration. On day 4, the patient's GCS score dropped to 3 hence he was intubated for cerebral and airway protection. His blood pressure dropped to 89/59 mmHg, requiring IV noradrenaline 5ml/h for hemodynamic support.

On day 5, the patient was transferred to General Intensive Care Unit (GICU). He was treated for septic shock with IV meropenem 2 g three times daily, IV azithromycin 500 mg daily and IV hydrocortisone 50 mg four times daily. The ECG examination revealed a temporary T wave depression. The patient continued to have low GCS score and elevated random blood sugar (greater than 13.0 mmol/L) for 5 days. On day 6, the CK level decreased to 633 U/L. The result of serum lithium level taken on day 3 was received on day 7 and it showed severe toxicity (3.2 mEq/L). The patient was given hemodialysis (HD) for 3 hours and subsequently the lithium level returned to normal (table 1). His body temperature was normalized on day 8. On day 10 the patient regained consciousness but was not responding to commands. He was extubated on day 11 and was transferred to neuromedical ward. He was improving in the ward, with full GCS score by day 14. The CK level also dropped to 302 U/L on the same day. The lithium toxicity was completely resolved on day 16. He was discharged with haloperidol 3 mg twice daily and sodium valproate 600 mg twice daily for his bipolar disorder management. Other discharged medications were aspirin 100 mg once daily, clopidogrel 75 mg once daily and metformin 1 g twice daily. The patient was given appointment date in 2 weeks time.

**Table. 1:** Lithium level sampling time and results.

Date of sampling	Time of sampling	Source	Date of results received	Results (mEq/L)
Day 3	3.23 pm	Blood	Day 7	3.2
Day 7	2.15 pm	Blood (pre HD)	Day 7	0.7
Day 7	6.15 pm	Blood (post HD)	Day 7	0.5
Day 10	11.30 am	Blood	Day 10	0.3

HD: hemodialysis

### DISCUSSION

Lithium and antipsychotic combination has been used to treat the bipolar disorder, although this combination has the potential to cause reversible to irreversible neurotoxicity (Baastrup *et al.*, 1976; Cohen and Cohen, 1974). The exact mechanism is unknown, but it has been postulated that this combination may cause toxicity by increasing dopamine receptor blockade (Boora *et*

*al.*, 2008; Friedman and Gershon, 1973) or by changing lithium pharmacokinetic resulting in increasing intracellular level (Boora *et al.*, 2008). In a previous case report, a healthy elderly male with bipolar disorder type 1 (manic episode with psychotic features) was prescribed risperidone 2 mg once daily in addition to lithium carbonate 450 mg twice daily to control the manic symptom. Four days after the treatment, the patient experienced fever, confusion, generalized weakness, tremor at rest, rigidity and masked facial expression. The significant laboratory test findings were lithium level of 1.47 mEq/L and white blood cell count of  $20.3 \times 10^3/\text{mm}^3$ . Lithium and risperidone were discontinued and his conditions improved after a few days (Boora *et al.*, 2008). Our patient had been prescribed risperidone with lithium for the past 9 months and the tremor that appeared approximately 25 days before the hospital admission could be associated with this combination. Risperidone is one of the possible precipitating factors in the present lithium toxicity case.

Apart from risperidone, the use of telmisartan in our patient may have contributed to the lithium toxicity. Drug interactions of ARB with lithium have been documented (Ma *et al.*, 2012; Su *et al.*, 2007). There were 2 case reports which described lithium toxicity subsequent to initiation of valsartan and telmisartan respectively in patients on long term lithium therapy. ARB blocks angiotensin II type I receptor (AT1), hence causing decreased sodium reabsorption at proximal tubule, leading to natriuresis and subsequently hyponatremia. Natriuresis is compensated by increased renal sodium reabsorption at the proximal tubular site. Since lithium is reabsorbed concurrently through this pathway, the serum lithium level increases gradually and results in toxicity (Ma *et al.*, 2012; Su *et al.*, 2007). The hyponatremia presented in our patient upon admission suggests that interaction has occurred between telmisartan and lithium. This supposition is reasonably supported by the patient's clinical condition of mild tremor since the initiation of telmisartan therapy.

Interactions of risperidone and telmisartan with lithium play certain roles in precipitating our patient to the lithium toxicity. However, SSRI is the major provoking drug that caused the lithium poisoning in accordance to the onset of the toxicity clinical manifestations. In a previous case report, a 44-year-old woman with bipolar disorder well maintained on lithium carbonate 1200 mg/day experienced severe lithium toxicity after being added on fluoxetine 20 mg/day. She was presented with neurological symptoms of ataxia, dizziness, unsteady gait and dysarthric speech within a few days after initiation of fluoxetine. Her serum lithium level was found to have increased to 1.7 mEq/L. The neurological symptoms resolved within 7 days after discontinuation of fluoxetine and dose reduction of lithium carbonate to 900 mg/day (Salama and Shafey, 1989). As compared to the above mentioned case, our patient had faster onset of neurological symptoms and higher level of serum lithium. Besides, both ataxic symptoms and serotonin syndrome were experienced by our patient. Imbalance of dopaminergic and cholinergic transmitters in the brain induced by SSRI is a possible explanation for the ataxic symptoms (Salama and Shafey, 1989). Lithium increases 5-hydroxytryptamine

(serotonin) metabolites in the CSF, therefore lithium can interact with SSRI and cause serotonin syndrome (Gill *et al.*, 2003).

Our patient was prescribed with risperidone for 9 months, telmisartan for around 1 month and fluvoxamine for 1 day along with increased dose of lithium for 9 months. The Drug Interaction Probability Scale (DIPS) was used to evaluate drug interaction causation in our patient (Horn *et al.*, 2007). The results showed a possible causal relationship (score of 4) between fluvoxamine and lithium. Telmisartan and risperidone were also found to have possible interactions with lithium, with the DIPS score of 4 and 3 respectively. Interactions between these drugs clearly precipitated our patient to experience chronic lithium toxicity with a level of 3.2 mEq/L. Other concurrent drugs were not found to have interactions with lithium. Chronic toxicity happens in patients on chronic lithium therapy and the severity is categorized as mild (1.5 to 2.0 mEq/L), moderate (2.0 to 2.5 mEq/L) or severe (greater than 2.5 mEq/L) based on the serum lithium concentration (Timmer and Sands, 1999). Severe toxicity is associated with serious morbidity and possibly mortality (Okusa and Crystal, 1994; Timmer and Sands, 1999). Our patient was in coma for a few days but managed to survive with appropriate management. The CNS effects of lithium toxicity predominate in severe cases (Horn, 2007), as seen with our patient who experienced serotonin syndrome (agitation and restlessness), tremor and mental status changes. Other clinical manifestations of our patient included vomiting, diarrhea, hyperthermia, dehydration, hypotension, ECG changes, thyroid dysfunction (decreased level of TSH) and myopathy (raised CK level).

Lithium toxicity is a serious medical problem. Hemodialysis is the cornerstone of therapy for severe lithium toxicity and should be performed in any patient who presents with coma, convulsions, respiratory failure, deteriorating mental status or renal failure irrespective of the serum lithium level (Timmer and Sands 1999). Lithium clearance is increased with hemodialysis. A previous case series reported that lithium clearance by dialysis ranged between 63 and 114 ml/minute compared with a clearance of 13 to 56 ml/minute in patients not receiving dialysis (Jaeger *et al.*, 1993).

The lithium half lives during dialysis ranged from 3.6 to 5.7 hours which is shorter than 15.9 to 36.8 hours in patients not receiving hemodialysis (Jaeger *et al.*, 1993). Our patient received hemodialysis as he was in coma and had declining mental status. Even though hemodialysis was delayed in our patient, he still had good response with significant improvement in mental status 3 days post hemodialysis.

## CONCLUSION

The concurrent use of antipsychotic, ARB, SSRI with lithium may possibly cause severe lithium toxicity. Discontinuation of the offending drugs and lithium plus hemodialysis therapy resulted in resolution of the toxicity in the present case. Clinicians should be aware of this potential drug interactions and avoidance of these combinations is preferable.

## CONFLICTS OF INTEREST

All the authors have no conflict of interest in connection with this paper. This case report did not receive any funding from any organization.

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