Lithium toxicity at therapeutic doses as a fallout of COVID-19 infection: a case series and possible mechanisms

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Lithium, a mood stabilizer used in the treatment of bipolar disorder is known for its anti-inflammatory properties with the discussion of its potential use in COVID-19 infection. The SARS-CoV-2 virus causing COVID-19 infection is known to enter the target cells through angiotensin converting enzyme-2 receptors present in abundance in the lung and renal tissue. Recent research supports the evidence for direct renal injury by viral proteins. Here we report two patients with bipolar disorder presenting with lithium toxicity in the presence of COVID-19 infection. Two patients with bipolar disorder, maintaining remission on lithium prophylaxis, presented to the psychiatric emergency with recent-onset fever and altered sensorium. Both the patient's investigations revealed lithium toxicity, elevated serum creatinine, urea and inflammatory markers. Hypernatremia, hyperkalaemia, and hyperchloremia were seen in one patient. Lithium and other psychotropic medications were stopped immediately, and COVID-19 treatment was initiated. Patient with clinical signs of lithium toxicity, hypernatremia, hyperkalaemia, and hyperchloremia developed ventricular tachycardia. He survived and regained consciousness after 2 weeks of aggressive conservative management. However, another patient died of acute respiratory failure on day 3. Possible direct infection of the kidney by SARS-CoV-2 viral proteins can manifest with acute kidney injury and lithium toxicity among patients on long-term lithium therapy. Health professionals treating COVID-19 infection among individuals on lithium therapy should be aware of the possibility of lithium toxicity in the background of renal inj ury. *Int Clin Psychopharmacol* 37: 25–28

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Introduction

Lithium is one of the first-line drugs used in the management of bipolar affective disorder (BPAD) (Malhi *et al.*, 2020). Lithium is almost completely absorbed from the intestinal tract, does not bind to plasma proteins, gets distributed in the extracellular fluid initially, and then gradually gets accumulated in the tissues (Goodman and Gilman's The Pharmacological Basis of Therapeutics, 2010). Lithium freely crosses the glomerular membranes and 80% is reabsorbed by diffusion in the proximal convoluted tubules and ninety-five percent is excreted unchanged through the kidneys (Grandjean and Aubry, 2009).

Lithium has a narrow therapeutic index, and among long-term users, there is a considerable risk of chronic kidney diseases such as nephrogenic diabetes insipidus and tubulointerstitial nephritis. In addition, renal tubular acidosis, hypercalcemia, hypernatremia are the manifestations of long-term lithium exposure (Félix *et al.*, 2010). SARS-CoV-2 infection in the current pandemic is predominantly known to affect the lungs. However, evidence suggests that it can affect the nervous system, cardia, gastrointestinal tract, and renal systems (Jain, 2020).

Initially, it was proposed that lithium might have a beneficial effect in patients with SARS-CoV-2 infection with some anti-inflammatory actions. Downregulation of glycogen synthase kinase 3-beta (GSK), a pro-inflammatory protein that increases the expression of IL-6 and TNF-alpha, implicated in the cytokine storm syndrome (Bou Khalil, 2020; Rajkumar, 2020; Rudd, 2020; Liu *et al.*, 2021; Snitow *et al.*, 2021; Theotonio dos Santos *et al.*, 2021), and suppression of NOD-like receptor family pyrin domain containing-3 (NLRP3) inflammasome activity, inhibition of cell death, and immunomodulation via membrane depolarization (Qaswal *et al.*, 2021) were the proposed protective mechanisms.

However, contrasting observations have been made in two patients with psychiatric illness on lithium, who developed toxicity after being infected with SARS-CoV-2 (Suwanwongse and Shabarek, 2020). Here we report two patients diagnosed with the bipolar affective disorder (BPAD) in remission on prophylactic lithium, presenting

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to emergency with signs and symptoms of lithium toxicity with SARS-CoV-2 infection.

Patient 1

Mr R, a 51-year-old married man with BPAD for 28 years, presented to the psychiatric emergency with disorientation, unsteadiness of gait, slurred speech, and difficulty getting up from the bed for the last 3 days. He also had fever, malaise, and two episodes of loose stools 2 days before the onset of the above symptoms. He has been in remission with Lithium 1350 mg/day and Valproate 1500 mg/day for the past 4 years. He was also on thyroxine replacement therapy (25 µg/day) for secondary hypothyroidism. He had a seizure in the past and has been seizure free for 20 years.

In the emergency room, he was found to be restless, disoriented to time, place, and person, febrile with a temperature of 103°F, pulse rate 94 bpm, respiratory rate – 22/min, BP – 164/114 mmHg, SpO_2 – 87%. Bilateral deep tendon reflexes were 2+ and had truncal and gait ataxia. Other systemic examinations were within normal limits. RT-PCR was found to be positive for SARS-CoV-2. Serum lithium was 2.6 mmol/l, serum creatinine 2.1 mg/dl, serum sodium 151 mmol/l, and potassium was 5.56 mmol/l. Serum valproate, calcium, phosphorus, plasma ammonia, and ECG were normal. Table 1 provides details on serial observations of serum lithium, renal function tests and serum electrolytes. (see Table, Supplemental digital content 1, *http://links.lww.com/ICP/A89*, which illustrates serial observation of all the blood parameters observed in the Patient 1). A high-resolution CT scan (HRCT) chest showed a CORADS (COVID-19-Reporting and Data System) score of 5, suggestive of SARS-CoV-2 infection. CT brain (plain) was normal. He was shifted to designated COVID ICU with a clinical impression of pneumonia due to SARS-CoV-2 infection, lithium toxicity, hypernatremia, and acute kidney injury (AKI) with a severe category of COVID-19 infection (*Revised National Clinical Management Guideline for COVID-19*, 2020).

All psychotropics were stopped. Treatment initiated included Ceftriaxone 1 g/i.v. twice daily, Ivermectin 12 mg BD for 5 days, T. Zinc 50 mg OD and T. Vitamin C 500 mg BD, dexamethasone 4 mg/i.v. BD and unfractionated heparin 5000 IU/SC, according to the protocol for management of COVID-19 infection (*Revised National Clinical Management Guideline for COVID-19*, 2020). Hypernatremia was managed with intravenous fluid 0.45% normal saline and 2% dextrose with eight units of insulin/day. His urine output was around 1–1.5 l/day. On day 4, patient had ventricular tachycardia, possibly due to elevated potassium, which was treated with calcium polystyrene sulphonate oral formulation. Urine output improved by day 10, regained consciousness by day 14 and by day 17, he regained orientation. However, he continued to have gait and truncal ataxia at the time of discharge from ICU with intention tremors and past pointing.

Patient 2

A 61-year-old married male diagnosed with BPAD for the past 8 years and diabetes mellitus, hypertension for the last 5 years and in remission with lithium 900 mg/day, quetiapine 300 mg/day and monthly injection of Flupenthixol 40 mg for the past 4 years. His wife brought him with 3 days history of fever and a 1-day history of altered sensorium. There was no history of substance use.

On examination, the patient was disoriented to time, place, and person and arousable on painful stimulus. He was febrile (temp – 100°F), pulse rate – 124 bpm, BP – 173/103 mmHg, SPO_2 was 96% with normal ECG. His cardiovascular and respiratory system examination were within normal limits. He tested positive for SARS-CoV-2 on RT-PCR. His serum lithium was 2.79 mmol/l, s. creatinine 2.2 mg/dl, s. urea 60 mg/dl, and the total white blood cell count was 19 200 cells/mm^3 with neutrophils 79% and lymphocytes 8.4%. The patient was diagnosed to have lithium toxicity with AKI with moderate SARS-CoV-2 infection.

A high-resolution CT scan of the chest showed a CORAD score of 5, and CT scan of the brain showed calcified granuloma of the right frontal lobe. We stopped all psychotropic medications. Treatment initiated included Ceftriaxone 1 g/i.v. twice daily, Ivermectin 12 mg BD for 5 days, T. Zinc 50 mg OD and T. Vitamin C 500 mg BD according to the protocol for managing the COVID-19 infection (*Revised National Clinical Management Guideline for COVID-19*, 2020). On the day of admission, in liaison with the medical team, he received 3 l of intravenous normal saline to treat lithium toxicity. However, on day 2, his SPO_2 dropped to 80% at room air and 92% at 10 l non-rebreathing mask (NRBM). His plasma D-dimer was 3567 and CRP was 50; On day 3, serum creatinine and urea

Table 1 Serial observation of lithium and renal function in the patient 1

Investigations unit (reference)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 13	Day 18
Lithium mmol/l (0.6–1.2)	2.6	2.39	1.98	1.18				0		0
Creatinine mg/dl (0.7–1.2)	2.1	3.1	2.4	1.9	1.6	1.3	1.6	1.3	2.3	1.3
Urea mg/dl (16.6–48.5)	52	75	94	94	78	68	71	61	101	66
Sodium mmol/l (136–145)	151	152.4	148.4	149.1	149	154	161.7	163	163.2	147.6
Potassium mmol/l (3.5–5.1)	5.56	5.85	6.34	5.68	4.91	5.18	4.43	4.86	3.86	3.67
Chloride mmol/l (98–107)	118.6	120.0	119.2	119.9	118.5	123.3	131.1	134.9	131	115.1

levels were 1.4 mg/dl and 87 mg/dl; the total count was 17.890 cell/mm^3, neutrophils 75%, and lymphocytes 10.3%. However, the patient did not show any improvement clinically and, complicated by acute respiratory failure, died on third day of admission.

Discussion

Patients described above highlight the presentation of lithium toxicity at therapeutic doses in individuals maintaining well on lithium and developing toxicity after SARS-CoV-2 infection. The first patient had no comorbid medical conditions, whereas the second patient had comorbid hypertension and diabetes mellitus. Both presented to our emergency room with a history of recent onset fever and altered sensorium. The first patient had some clinical signs of lithium toxicity. However, in the second patient, there were no obvious clinical signs of lithium toxicity.

The current second wave of the pandemic mandated us to screen all symptomatic psychiatric patients visiting the emergency room for SARS-CoV-2 infection who required inpatient care. Rapid progression of symptoms from the onset of fever to altered sensorium or unsteadiness of gait, slurred speech, and difficulty maintaining posture in a psychiatrically stable patient warned us to evaluate for serum lithium, electrolytes, and renal functions apart from routine biochemical evaluation.

On initial evaluation, both our patients had lithium levels in the toxicity range, deranged renal functions, and elevated inflammatory markers related to SARS-CoV-2 infection. The rapid onset of deranged renal function in a previously normal individual with toxic lithium levels indicates renal damage. The first patient had additional hypernatremia, hyperkalaemia, and hyperchloremia, but the second patient had normal serum electrolytes. The persistence of electrolyte imbalance in Patient 1 is suggestive of progressive renal injury. However, in the second patient, there could be a possibility of fluid overload (during correction of lithium toxicity) in the presence of renal damage and additional respiratory failure leading to death on day 3.

The rapid onset of renal failure in the febrile illness of SARS-CoV-2 origin indicates possible direct renal damage by the virus. It has been noted that the S1 domain of the SARS-CoV spike protein binds to the angiotensin converting enzyme 2 (ACE2) receptor to enter into human cells (Li *et al.*, 2003). Full-length genomic sequencing of SARS-CoV-2, i.e. COVID-19 virus, is 79.5% homologous to SARS-CoV (Zhou *et al.*, 2020). The target cells human ACE2 is not only expressed in lung tissue but can also be detected in the kidneys, mainly in proximal tubules, afferent arterioles, collecting ducts, and the thick ascending limb of Helen (Santos *et al.*, 2013). SARS-CoV-2 nucleic acid has been detected in urine samples of 6.9% of the infected patients suggesting that the kidney might be the new target for this novel virus (Ling *et al.*, 2020). Functional renal impairment among patient with SARS-CoV-2 infection varies from 3.2% to 28.5% (Wang *et al.*, 2021). Based on the autopsy finding of six patients who died of renal impairment with COVID-19 infection, immunohistochemistry examination of the renal tubules have revealed accumulation of the nucleocapsid protein antigen of SARS-CoV-2 in the cytoplasm of kidney tubules instead of glomeruli (Diao *et al.*, 2021). In another autopsy study, three patients out of six demonstrated SARS-CoV-2 virus particles in the cytoplasm of renal proximal tubular epithelium and podocytes (Su *et al.*, 2020). These studies indicate that COVID-19 patients can develop acute renal injury due to direct viral infection of the kidney. The other postulated mechanism for acute renal injury is the immune-mediated response, cytokine storm syndrome characterized by elevated TNF-α, IL-1, IL-6, interleukin (IL)-12, and interferon (IFN)-α by the host immune system, which leads to multiple organ failure including kidney (Iannaccone *et al.*, 2020). The acute renal damage in patients with SARS-CoV-2 infection could also be due to dehydration, electrolyte and acid-base imbalance, hypotension, cardiac insufficiency, disseminated intravascular coagulation, drugs like NSAIDs, antibiotics, and antiviral drugs (Qian *et al.*, 2020).

In the kidneys, similar to sodium ions, lithium freely crosses the glomerular membranes, 80% is reabsorbed by diffusion in the proximal tubules and 95% of lithium is excreted unchanged through the kidneys. Less than 1% is lost through feces and the rest 4–5% through sweating (Grandjean and Aubry, 2009). Lithium competes with sodium in the tubular reabsorption (Ward *et al.*, 1994). Long-term lithium therapy is also considered to cause hypernatremia through the central and peripheral diabetic insipidus and is considered one of the commonest causes for drug-induced hypernatremia (Hansen and Amdisen, 1978; Liamis *et al.*, 2009). It might be possible that in both our patients' long-term lithium had led to hypernatremia, or it might have exaggerated in the presence of acute renal injury.

Anti-inflammatory and neuroprotective effects of lithium are well-established. It has been established that lithium has renal tubular cell repair and regeneration effect on a murine model of cisplatin or ischemia/reperfusion-induced AKI through the inhibition of GSK3b (Bao *et al.*, 2014). However, such a model has not been tested in human trials; moreover, nephrogenic diabetic insipidus is evident in almost 50% of patients receiving prolonged lithium therapy (Jeffery *et al.*, 2007). The recent proposal by the researchers for the novel role of lithium as an antiviral agent against the SARS-CoV-2 virus is questionable as we are not clear as how long lithium treatment is needed to generate the anti-inflammatory property. Moreover, recent systematic review of six in vitro studies reporting on the influence of lithium on coronavirus

infections has concluded that lithium effectively inhibits coronavirus infection when administered at concentrations that are toxic to humans (Nowak and Walkowiak, 2020). Recently, lithium toxicity has been observed in two psychiatric patients on lithium therapy infected with SARS-CoV-2 (Suwanwongse and Shabarek, 2020).

Conclusion

Amidst the current COVID-19 pandemic, there could be a potential rise in the number of cases of lithium toxicity in patients who are on long-term lithium therapy with concomitant SARS-CoV-2 infection. It is necessary to monitor lithium levels more frequently in such individuals along with the examination of routine clinical and biochemical parameters to look for signs of lithium toxicity. It is also vital to educate health professionals and patients regarding the possibility of lithium toxicity in the event of SARS-CoV-2 infection.

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Conflicts of interest

There are no conflicts of interest.

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