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Synergistic risks: Lamotrigine induced rash potentiating lithium toxicity

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INTRODUCTION

Lithium and lamotrigine are mood stabilizers approved for the treatment of bipolar disorder. Lithium's narrow therapeutic index and comparatively minor alterations in plasma concentrations can have significant clinical sequelae (McKnight et al., 2012). Several classes of drugs have been implicated in developing lithium toxicity, including diuretics and nonsteroidal anti-inflammatory compounds (Finley, 2016). Lithium is not metabolized and is eliminated almost entirely via the renal route (Rust et al., 2018). Consequently, plasma concentrations are exquisitely sensitive to physiological factors affecting renal function, such as age, dehydration, and sodium imbalance. Sodium depletion can cause increased lithium reabsorption in the kidneys, potentially leading to toxicity (Joshi et al., 2019). Lamotrigine is known to carry the risk of causing rash, which in severe cases can be fatal. The rash leads to cutaneous and extracutaneous involvement, with impaired alimentation leading to fluid and electrolyte imbalance. In this case report, we present a patient prescribed a combination of lamotrigine and lithium. The patient developed rash due to lamotrigine, leading to lithium toxicity and acute kidney injury, emphasising the importance of monitoring patients closely when using these medications in combination.

CASE PRESENTATION

A 43-year-old male patient diagnosed with Bipolar Affective Disorder presented with rash in the Department of Psychiatry of a tertiary care hospital. His treatment regimen for bipolar disorder consisted of 1500 mg of Lithium Carbonate, 75 mg of Lamotrigine, and 10 mg of Olanzapine. Additionally, he had a medical history of type 2 diabetes mellitus and hypothyroidism, both of which were under the care of the Department of Medicine. The rash was widespread, affecting both the skin (with more than 30% coverage) and oral mucosa. Physical examination revealed diffuse, erythematous maculopapular rash. His vital signs were stable, and overall systemic examination showed no abnormalities. Consequently, he was managed within an inpatient setting with the consultation of the Department of Dermatology and Medicine. Given the suspicion of lamotrigine hypersensitivity, lamotrigine was promptly discontinued, and he

Table 1. Laboratory parameters

Laboratory parameters	Day 0 (Admission Day)	Day 9	Day 10	Day 12	Day 14	Day 17
Serum lithium (*n*=0.6-1.2 mmol/L)	0.86 mmol/L	3.41 mmol/L	3.00 mmol/L	2.81 mmol/L	1.60 mmol/L	0.59 mmol/L
Serum sodium (*n*=136-145 mmol/L)	138 mmol/L		129 mmol/L	130.38 mmol/L	143mmol/L	147mmol/L
Serum urea (n=10-45 mg/dl)	19 mg/dl		50.80 mg/dl	48.36 mg/dl	29.01 mg/dl	25.25 mg/dl
Serum creatinine (*n*=0.2-1.2 mg/dl)	1.06mg/dl		2.68 mg/dl	2.74 mg/dl	1.57mg/dl	1.13mg/dl

was initiated on a course of 40 mg of prednisolone. His serum lithium level at 1500 mg of lithium carbonate was 0.86 mmol / L and it was continued along with Olanzapine 10 mg. Importantly, the renal function test and serum electrolytes were within normal limits. Laboratory values are reported in Table 1.

Due to the involvement of oral mucosa, the patient experienced a decrease in oral intake during this period. In the first week of admission, he exhibited depressive symptoms, prompting the addition of 20 mg of fluoxetine to the treatment regimen. Notably, the erythema began to subside shortly after initiating corticosteroid therapy, and the skin lesions gradually disappeared with scaling. Over the next few days, he developed further dysphoria, downgaze eye, decreased spontaneity, and slowed reaction time mimicking a depressive presentation but without any depressive cognition. Considering cognitive impairment, a serum lithium estimate was conducted, revealing a level of 3.41 mmol / L. Notably, despite this elevated level, the patient did not exhibit any signs of neuromuscular toxicity. To confirm the lithium level, a repeat serum lithium estimate was performed, showing a level of 3.0 mmol/L. Other laboratory parameters were also assessed, indicating elevated serum urea and creatinine levels, hyponatremia, and fluctuating blood glucose, all of which indicated acute kidney injury. Importantly, the patient did not display any signs of lithium toxicity at this stage. The patient was managed conservatively by discontinuing lithium carbonate and ensuring adequate hydration. The patient's care during this period was carried out in consultation with the department of general medicine.

One week later, of raised serum lithium levels and a deranged renal function test, the patient displayed a new set of symptoms. These included polyuria, polydipsia, dysarthria, cogwheel rigidity, mild tremors, and disorientation to time, place, and person. Considering risk of further exacerbating hyponatremia and extrapyramidal symptoms, fluoxetine and olanzapine were discontinued. The patient was started on a gradually increasing dose of tablet quetiapine initiated at a dose of 25 mg. At the same time, the patient was kept on intravenous fluids to address polyuria and polydipsia, and over the following days, there was a noticeable improvement. Approximately one week later, there was a positive transformation in the patient's condition. Disorientation and dysarthria resolved, and polyuria and polydipsia gradually improved. Furthermore, the patient's activity level, eye contact, and social interaction improved, and the mood stabilised into a euthymic state.

DISCUSSION

The rash is a common side effect associated with lamotrigine and it is of paramount concern among all the potential adverse effects (Kanner, 2005). Notably, in addition to developing skin lesions, lamotrigine-related rashes can extend to areas beyond the skin, leading to painful erosion of various mucosal surfaces (Roujeau & Stern, 1994). When this rash involves the gastrointestinal mucosa, it can disrupt normal feeding patterns, resulting in fluid and electrolyte imbalances (Roupe et al., 1986). In a notable case report by Schaub et al. in 1994 (Schaub et al., 1994), lamotrigine was associated with renal failure, further emphasizing the serious nature of its potential side effects.

Being a monovalent cation, lithium is not metabolized in the body and is excreted primarily through the kidneys. The kidneys treat lithium and sodium similarly, so if there is sodium depletion, the reabsorption of lithium significantly increases, leading to the accumulation of lithium in the body. Any condition which leads to sodium and volume depletion like vomiting, diarrhoea, fever, renal insufficiency, excessive exercise, water restriction, excessive sweating, and low sodium diet may enhance lithium reabsorption in the kidneys. In our patient, rash induced by lamotrigine led to oral mucosal involvement, disrupting his oral intake. This disruption in oral intake had a cascading effect, ultimately resulting in an imbalance in the body's sodium levels, leading to hyponatremia. Since our patient was concurrently taking lithium carbonate, the hyponatremia caused the body to prioritise lithium retention over sodium. This led to an increase in the blood levels of lithium and, subsequently, the development of lithium toxicity. Furthermore, kidney involvement due to lamotrigine-induced hypersensitivity resulted in elevated urea and creatinine levels, further exacerbating the lithium toxicity. Therefore, when considering the combination of lamotrigine and lithium carbonate, caution should be exercised regarding the risk of lithium toxicity, particularly when the patient's fluid status is altered due to rash.

This is also to mention here that caution should also be exercised when olanzapine and fluoxetine are given along with lithium and lamotrigine in the clinical context mentioned above. The oral mucosal rashes due to lamotrigine caused reduced oral food and water intake and thus hyponatremia. Selective serotonin reuptake inhibitors (SSRI) like fluoxetine are also known to cause/ exacerbate hyponatremia(Zhao et al., 2023). A co-prescription of Fluoxetine, lamotrigine, and lithium can cause elevated serum lithium levels, thus inducing lithium toxicity.

CONCLUSION

It's essential to recognize that lamotrigine's impact is not limited to causing skin lesions but can also extend to internal organs, such as the kidneys. This underscores the importance of vigilant monitoring and a thorough understanding of potential interactions when using these medications (lithium and lamotrigine) in combination.

Ethical Considerations: Does this study include human subjects? YES. Authors confirmed the compliance with all relevant ethical regulations.

Conflict of interest: No conflict of interest

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