e-ISSN: 2980-0463
Anat. J. Pharm. Sci., 2024:3(2)
AJPS
Case Report

Lithium Toxicity Due to Drug-Drug Interactions: A Case Report

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ABSTRACT: Lithium has a relatively narrow therapeutic range. As a result of drug-drug interactions, the blood level of lithium is highly affected. Drug-induced lithium toxicity and therapy are discussed in this case. A 37-year-old woman with bipolar illness, essential hypertension, hypothyroidism, unipolar depression, and schizoaffective disorder was admitted to the emergency department with hand numbness, tremor, agitation, and tachycardia. Due to a history of lithium use, her blood lithium concentration was measured and found to be 1.7 mmol/L. As a result, lithium treatment was suspended, and she was hospitalized in the intensive care unit with a diagnosis of lithium toxicity. Lexicomp® drug interaction database was examined by the clinical pharmacist. Candesartan, hydrochlorothiazide, and dexketoprofen caused toxicity. The clinical pharmacist advised stopping the existing antihypertensive regimen and starting amlodipine, as it did not interact with lithium, reducing its levels to 1.4-1.2 and 0.8 mmol/L, respectively. Clinical pharmacist treated drug-induced lithium toxicity.

Keywords: *drug-drug interactions, lithium, pharmacy, toxicity*

1 INTRODUCTION

Lithium is a mood-stabilizing medication used primarily in the treatment of bipolar disorder (1). In the treatment of bipolar disorder, the therapeutic drug trough level of lithium is desired to be between 0.8-1.2 mmol/L in acute mania episodes and 0.6-1 mmol/L in maintenance treatment (2). In this case report, a patient who developed lithium toxicity due to drugs interacting with lithium and the management of drug-drug interactions is presented. Informed consent was obtained from the patient for this study.

2 CASE PRESENTATION

A 37-year-old woman with a history of bipolar affective disorder (8 years), essential hypertension (5 years), hypothyroidism (4 years), unipolar depression (9 years) and schizoaffective disorder (1 year) presented with numbness and tremor in her hands, agitation and tachycardia. The patient was referred to the emergency room by her doctor due to her condition. Based on the patient's and her relatives' anamnesis, it was determined that the patient had no further complaints and maintained a regular sleep pattern. When

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Submitted: 20.08.2024 Accepted: 10.09.2024

the mental status examination was examined, it was seen that she was conscious, oriented and cooperative. Her associations were regular; her speech rate and amount were normal; she had no suicidal or homicidal thoughts; and she did not describe any delusions. The lithium blood level was found to be 1.7 mmol/L. Following the diagnosis of lithium toxicity, the patient was admitted to the anaesthesiology and reanimation intensive care unit (ICU) and lithium treatment was suspended. When the patient was admitted to the intensive care unit, her vital signs were as follows: blood pressure: 128/68 mmHg, pulse rate: 121 beats/min.

The medications used routinely by the patient were given together with their indications in the ICU:

- Aripiprazole 10 mg every 24 hours (q24h) and lithium carbonate 300 mg every 8 hours (q8h): Bipolar affective disorder
- Candesartan cilexetil + hydrochlorothiazide 32 mg/12.5 mg q24h: Essential hypertension
- Levothyroxine sodium 100 mcg q24h: Hypothyroidism
- Quetiapine fumarate 50 mg q24h: Schizoaffective disorders
- Dexketoprofen 25 mg: She takes it on demand every time she has pain

The potential drug-drug interactions were reviewed by clinical pharmacists using the Lexicomp® Drug Interaction Checker.

Three drug-drug interactions with a risk level of D that could increase lithium blood concentrations were identified. These:

1. Lithium + Candesartan: Although the interaction mechanism is not fully known, angiotensin receptor blockers increase the retention of lithium by inducing natriuresis. In patients taking angiotensin II receptor blockers (ARBs), it is recommended to start lithium at lower doses.
2. Lithium + Hydrochlorothiazide: Although the mechanism of interaction is not fully known, hydrochlorothiazide increases the proximate tubular reabsorption of lithium.
3. Lithium + Dexketoprofen: Although the mechanism of interaction is not fully known, NSAIDs (nonsteroidal anti-inflammatory drugs) reduce the renal clearance of lithium.

The clinical pharmacist reported these drug-drug interactions to the physician in charge of the ward and recommended that the current antihypertensive medication be discontinued for the duration of the ward stay and amlodipine 10 mg q24h be given as an antihypertensive that does not cause any interaction, which the physician did. Samples were taken for lithium blood levels the day after the change in treatment. These showed concentrations of 1.4–1.2 and 0.8 mmol/L, respectively. Lithium produces a therapeutic response with serum concentrations between

0.8 and 1.2 mmol/L in a patient receiving 300 mg three times daily, as in this case. It was unusual for this patient to have an initial measured lithium serum concentration of 1.7 mmol/L. Discontinuation of lithium treatment showed that lithium concentrations had decreased and remained at therapeutic levels. After discharge, the patient's lithium treatment was continued by the physician in charge.

In a written consultation note given to the patient and her relative by the clinical pharmacist, the following recommendations were made.

It was said that the increase in lithium levels occurred due to drug interactions and that the drugs causing these were candesartan + hydrochlorothiazide, an antihypertensive that the patient used routinely and dexketoprofen, which she used whenever she had pain.

Alternatively, as the patient's previous use of amlodipine caused ankle edema, the patient was told that lercanidipine 10 mg or 20 mg could be given if necessary as an antihypertensive that does not interact with lithium and causes less edema (3), and that she could use acetaminophen rather than dexketoprofen when she had pain. The patient was discharged on the third day of hospitalisation with improvement in symptoms. When the patient was contacted 1 week after the discharge, she shared the consultation note written by the clinical pharmacist with her doctor during the internal medicine clinic control and it was learnt that lercanidipine 10 mg q24h was prescribed as antihypertensive.

3 DISCUSSION

Currently, lithium is considered the primary choice for preventing bipolar disorder. However, using this medicine safely and effectively requires a thorough understanding of its pharmacokinetics, potential adverse effects, and the relative risk of drug-drug interactions (4). Lithium blood levels may vary depending on drug-drug interactions. While some interactions reduce lithium blood levels, some interactions lead to an increase, and as a result of this increase, intoxication may even occur. Our patient also had tachycardia and numbness in the hands due to lithium toxicity that developed as a result of drug-drug interactions. Drug groups that cause an increase in lithium blood levels include diuretics, NSAIDs and angiotensin-converting enzyme (ACEi) inhibitors (5). Lithium levels showed a clear relationship with gender, that women having higher values. However, only NSAIDs were found to have the ability to independently increase lithium levels (6). Although the interactions between these drugs and lithium are not contraindicated, lithium levels should be closely monitored due to the risk of occurrence of changes in lithium blood levels.

Due to the narrow therapeutic range, even slight changes in lithium concentration can cause serious side effects. Many case reports in the literature emphasize that ACEi (7), NSAIDs (8) and thiazide diuretics (9) may increase lithium reabsorption and thus increase blood lithium concentrations. In this case, several medications may have played a role in lithium toxicity. The patient was on a combination of candesartan and hydrochlorothiazide. Since the medications in this combination have a similar effect in increasing lithium blood concentrations, they exacerbate the situation. In addition, the patient was taking NSAID pain relievers. NSAIDs decrease glomerular filtration rate by inhibiting prostaglandin synthesis. In our case, these mechanisms led to decreased lithium excretion and increased blood levels. This toxicity was effectively managed by changing the drugs.

4 CONCLUSION

Based on the presented case, it is understood that patients receiving lithium therapy should be informed about drug-drug interactions and that caution is required. Due to the narrow therapeutic dose range of lithium, it is important to closely monitor it for toxicity and carefully evaluate any reported indications of toxicity. Attention should be paid to the initiation of additional medication, or the use of non-prescribed medication and it should be remembered that the patient should be informed about the symptoms of poisoning. Pharmacists play a crucial role in minimizing the potential negative consequences of drug-drug interactions through providing of information to patients, their relatives, and healthcare professionals.

5 AUTHOR CONTRIBUTIONS

Design: M.S.T., K.K.; Resources M.S.T., A.Ç.; Data collection: M.S.T.; Writing: M.S.T., K.K., A.Ç., N.Ö.A.; Critical Review: A.Ç., N.Ö.A.

6 CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

7 REFERENCES

[1] Malhi GS, Gessler D, Outhred T. The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. J Affect Disord. 2017;217:266-80.

[2] Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170.

[3] Skovbjerg BK, Helgestad OK, Oxlund CS, Christensen B, Henriksen JN. [Not Available]. Ugeskr Laeger. 2023;185(16).

[4] Finley PR. Drug interactions with lithium: an update. Clinical Pharmacokinetics. 2016;55(8):925-41.

[5] Ferensztajn-Rochowiak E, Rybakowski JK. Long-term lithium therapy: side effects and interactions. Pharmaceuticals. 2023;16(1):74.

[6] Scherf-Clavel M, Treiber S, Deckert J, Unterecker S, Hommers L. Drug-Drug Interactions Between Lithium and Cardiovascular as Well as Anti-Inflammatory Drugs. Pharmacopsychiatry. 2020;53(5):229-34.

[7] Spinewine A, Schoevaerdts D, Mwenge GB, Swine C, Dive A. Drug-induced lithium intoxication: a case report. J Am Geriatr Soc. 2005;53(2):360-1.

[8] De Winter S, Meersseman W, Verelst S, Willems L, Spriet I. Drug-related admissions due to interaction with an old drug, lithium. Acta Clinica Belgica. 2013;68(5):356-8.

[9] Handler J. Lithium and antihypertensive medication: a potentially dangerous interaction. J Clin Hypertens (Greenwich). 2009;11(12):738-42.