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## DRUG-INDUCED LITHIUM INTOXICATION: A CASE REPORT

*To the Editor:* In their recent observation study, Juurlink et al. reported that the risk of lithium toxicity dramatically increased within a month of initiating treatment with a loop diuretic or an angiotensin-converting enzyme (ACE) inhibitor.<sup>1</sup> Besides pharmacokinetic drug interactions, interactions with psychotropic medications have been attributed to pharmacodynamic mechanisms.<sup>2</sup> We report a case of hospital admission for lithium toxicity secondary to drug interactions.

### CASE REPORT

A 74-year-old woman was referred to us for a 3-week history of functional decline, lethargy, confusion, diarrhea, tremor, and dysarthria. Medical history included bipolar disorder, type II diabetes mellitus, hypertension, and ischemic heart disease. Medications on admission were lithium (250 mg three times daily), escitalopram (10 mg daily), levomepromazine (6.25 mg daily), lormetazepam (2 mg daily), metformin (850 mg three times a day), repaglinide (1 mg twice daily), lisinopril (30 mg daily), irbesartan (300 mg daily), furosemide (30 mg daily), and spironolactone (50 mg daily).

On admission, the patient was drowsy and confused. Glasgow Coma Scale was 12 of 15. Neurological examination showed dysarthria but no focal neurological deficits. Lithemia was 2.3 mEq/L (therapeutic range 0.6–1.2 mEq/L). Other investigations, including laboratory tests, computed tomography scan, and electroencephalogram, were not contributive. Serum creatinine was 161  $\mu$ mol/L with an estimated clearance of 34 mL/min, secondary to dehydration.

Three months before admission, lisinopril dosage had been increased from 20 mg to 30 mg daily and irbesartan added for hypertension. Seven weeks before admission, spironolactone had been added. In addition, dextemide 0.50 mg (a centrally acting anticholinergic drug licensed for the treatment of neuroleptic-induced extrapyramidal symptoms) had been recently added for worsening tremor, but no improvement was observed. Confusion had increased, and the drug was discontinued.

On admission, lithium was withdrawn, as were diuretics, levomepromazine, and escitalopram. Risperidone (0.25 mg twice daily) was added, but neurological status deteriorated with increased agitation, although the lithium

level had fallen to 1.2 mEq/L on the fourth day after admission. Upon consultation, the clinical pharmacist proposed stopping potentially interacting drugs (lisinopril, irbesartan, risperidone) to accelerate lithium excretion and to eliminate neurotoxic symptoms. The patient was simultaneously transferred to the intensive care unit because of apathy and oliguria. Rehydration and withdrawal of interacting drugs led to substantial neurological improvement. The patient was discharged 2 weeks later on carbamazepine for maintenance treatment of bipolar syndrome. Two months later, the patient remains stable.

### DISCUSSION

Risk factors for lithium toxicity include age-related altered pharmacokinetics, polypharmacy, and renal impairment. This case highlights the importance of stopping the causal drug but also drugs that may delay lithium elimination or worsen neurotoxic effects. Several drugs may have played a role in lithium intoxication. ACE inhibitors enhance the tubular reabsorption of lithium, and diuretics promote renal sodium wasting. They increase the risk of hospital admission for lithium toxicity.<sup>1</sup> The outcome of concurrent use of lithium and spironolactone remains unclear.<sup>2,3</sup> The addition of an angiotensin-II receptor antagonist (irbesartan) several weeks before admission may have contributed to lithium intoxication. The three case reports with candesartan, losartan, and valsartan that have been published indicate that intoxication can take several weeks to develop fully.<sup>3</sup> The mechanism of interaction is probably at least partially similar to that with ACE inhibitors. Finally, escitalopram and levomepromazine used with lithium may have increased the tremor associated with these drugs used alone.<sup>4</sup> It is also possible that a neurotoxic reaction occurred after the addition of risperidone. A similar observation has previously been reported.<sup>3</sup>

The equilibration of lithium between plasma and brain is extremely slow. Understanding this delay better enables the clinician to care for patients with lithium toxicity. Because clearance from the plasma is much faster than from the brain, it is not uncommon for patients who have presented with chronic lithium toxicity to still have signs of neurological toxicity when lithium concentrations have fallen into or below the therapeutic range.<sup>5</sup> This was the case here.

Inadequate monitoring of drug therapy can lead to a phenomenon called the “prescribing cascade.”<sup>6</sup> The “prescribing cascade” begins when an adverse drug reaction is misinterpreted as a new medical condition. Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects. Dextemide was added for worsening tremor probably secondary to lithium overdosage unrecognized at that time. This led to worsening neurological status. Geriatricians should be aware that a delay of several weeks between the addition of a new drug and lithium intoxication is possible.<sup>2</sup> Lithemia and clinical signs of overdosage should be monitored accordingly.

This case also illustrates that the contribution of clinical pharmacists is valuable in reducing drug-related morbidity and optimizing drug therapy.<sup>7</sup>

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CARDIAC DYSFUNCTION WITH SEVERE ANEMIA IN AN AGED CASE

*To the Editor:* On April 16, 2002, an 88-year-old woman was admitted to our hospital with complaints of easy fatigability and exertional dyspnea. Anemic conjunctiva palpebrae and pretibial edema were noticed on admission. Laboratory findings on admission showed white blood cell count 4,880/ $\mu$ L, red blood cells  $131 \times 10^4$ / $\mu$ L, hemoglobin (Hb) 4.4 g/dL, hematocrit 12.9%, platelets  $25.7 \times 10^4$ / $\mu$ L, reticulocytes 0.1%, serum creatinine 0.9 mg/dL, and serum iron 171 microgram/dL. Erythropoietin was highly elevated (2,860 mU/mL). Bone marrow examination showed severe hypoplasia specific for erythroid line (erythroid 0%), suggesting a diagnosis of pure red cell aplasia. Chest roentgenogram showed an enlarged heart with a cardiothoracic ratio of 60% and presence of pleural effusion, suggesting impaired cardiac function by severe anemia. Electrocardiogram (ECG) showed no abnormality except low amplitude of T-waves. Ultrasonocardiogram revealed reduced left ventricular ejection fraction and left ventricular dilatation at diastolic phase. Chest computerized tomography revealed relatively enlarged thymic mass (3 x 3 cm) for her age. As blood transfusion was performed to raise Hb level to 7 g/dL, pleural effusion and exertional dyspnea disappeared. Thymectomy was performed for treatment of pure red cell aplasia. After the thymectomy, cyclosporine A was administered. Hb gradually rose and reached 8.5 g/dL to

9.5 g/dL, accompanying normalization of erythropoietin (EPO) level (~20 IU/L). Cardiac function was promptly recovered, as shown by chest roentgenogram, ECG, and ultrasonocardiogram (Figure 1). Pretibial edema decreased gradually but did not completely disappear at 10 g/dL of Hb. EPO injection of 6,000 IU per week was started. About a month later, Hb level reached 14.0 g/dL, at which point she revealed no edema at all. During the additive EPO treatment, Hb level was within a range of 11 g/dL to 14 g/dL, and the improved cardiac function was maintained.

Although anemia is prevalent in old age, the minimum physiologically required value of Hb is potentially modifiable. Anemia is defined according to World Health Organization (WHO) criteria as a concentration below 12 g/dL in women and below 13 g/dL in men. Some studies report a particularly notable increase in prevalence of anemia in the oldest subjects ( $\geq 85$ ).<sup>1-7</sup> Even though normal Hb level can be deduced from mean value of Hb level of a healthy aged population, it is still unclear whether the mean value reflects a physiologically sufficient Hb level for aged organs. The present case showed that cardiac function was mostly normalized at 8.5 g/dL of Hb but sufficiently recovered and maintained in a range from 11 g/dL to 14 g/dL. Eleven g/dL of Hb seemed to be the minimum required Hb level for maintenance of normal cardiac function in this patient. In the present case, cardiac malfunction under severe anemic condition was evidenced clearly using ultrasonocardiogram. Anemia is a known risk factor for ischemic heart disease. The reduction in oxygen delivery by erythrocytes with anemia may be a cause of more severe cardiovascular diseases.<sup>7,8</sup> Nevertheless, in this case with severe anemia, ECG did not seem to reveal characteristic changes for presumptive tissue hypoxia such as ST depression or inverted T-wave. It has been reported that anemic condition accompanies ST-T depression or inverted T-wave,<sup>9</sup> but correlation between T-amplitude and Hb has not been reported. In the present case, the ratio of amplitude of T/QRS complex (T/QRS ratio) increased as Hb level increased. Although the other ECG parameters, including heart rate, RR difference, QT interval, and QT dispersion, did not correspond to the

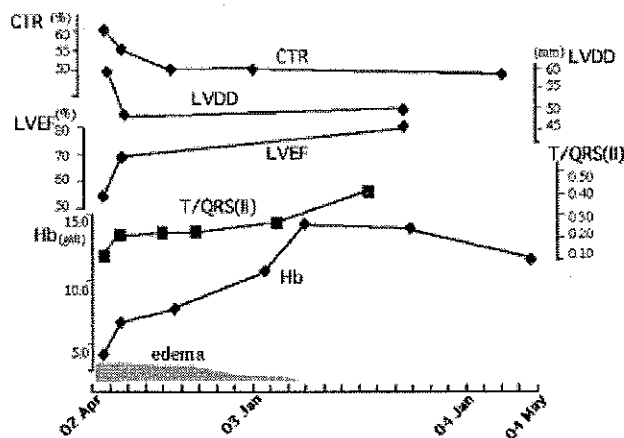


Figure 1. Cardiac function and hemoglobin (Hb) level. CTR = cardiothoracic ratio; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; T/QRS(II) = T-wave amplitude/QRS complex amplitude in lead II of the electrocardiogram.