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LETTER TO THE EDITOR

Current status of serum lithium concentration measurement in Japan

Lithium has been used to treat bipolar disorder.[1] Given the closeness between the therapeutic and intoxication ranges, caution is necessary to avoid the occurrence of lithium intoxication. In chronic lithium intoxication, severe adverse reactions (ARs) may occur, such as seizure, myoclonus, and atrioventricular block.[2,3]

In 2012, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan investigated the proper use of lithium and published an alert (https://www.pmda.go.jp/files/000153187.pdf). However, the number of patients seeking relief related to ARs caused by lithium has not decreased since then.[4] Failure to measure serum lithium concentrations in patients taking lithium may be considered inappropriate use of this drug.[5]

We aimed to evaluate the present status of serum lithium concentration measurement and examined factors related to serum lithium measurement by using a database produced by JMDC Inc. (https://www.jmdc.co.jp/wp-content/uploads/2019/11/news20180701.pdf) with real-world data in Japan. To our knowledge, this is the first study to use a real-world database to investigate the appropriate use of lithium in Japan. The Ethics Committee of the Nihon Pharmaceutical University determined that this study did not require ethical review, as the database does not contain personal information on patients.

The JMDC hospital-based database contains medical claims and Diagnosis Procedure Combination survey data collected from contracted hospitals since April 2014.[6,7] The most recent data include information on approximately 18 million patients and 453 hospitals. In this study, data on patients who were prescribed lithium between October 2021 and September 2022 were extracted from the database.

The lithium package insert states that serum lithium levels should be regularly measured once every 2–3 months during maintenance treatment, therefore we targeted patients with 60 or more lithium prescription days during the study period. Measurement of the serum lithium level was defined as having been performed if the drug-specific therapeutic management fee was recorded during the study period (i.e., the same definition as used in the PMDA survey). We evaluated demographic and clinical information on patients with serum lithium level measurements; analyses included data on sex, age when lithium was prescribed, lithium dose, whether the dose was changed, and concomitant medications. Patient ages were categorized into 10-year age groups. Lithium doses were analyzed using each patient's maximum dose during the study period, with a dose of 200–400 mg/day as the reference group.

During the 1-year study period, 2259 patients were prescribed lithium for 60 days or more; serum lithium levels were measured for 967 of these patients (42.8%). This is slightly lower than the 48% of patients prescribed lithium who had lithium levels measured per results of the 2012 investigation by the PMDA. The characteristics of patients prescribed lithium in this study population are presented in Table 1. Serum lithium measurement was significantly more common among patients with dose changes and among those prescribed higher doses, suggesting that measurement of serum lithium concentration was not performed in patients without dose changes. Furthermore, among patients with dose changes, the percentage of those with serum lithium measurement performed was significantly higher among patients in the >400 mg group compared to the ≤400 mg group (70.0% vs. 49.5%, respectively, odds ratio 2.38, 95% confidence interval 1.47–3.87).

As noted in the alert from the PMDA, particular attention should be given to increased serum lithium levels in patients with poor dietary and/or fluid intake and those vulnerable to dehydration (e.g., elderly patients), regardless of whether any dose change has occurred. Serum lithium levels can increase with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics.[8] The present study indicates that serum lithium concentrations are not regularly measured, even with concomitant use of drugs associated with increased risk of serum lithium elevation. Patients should be adequately alerted to this risk in relation to NSAIDs, as these drugs are sometimes used in combination with other medications in both hospital prescriptions and over-the-counter medications. Also, patients with kidney failure should be cautioned about the occurrence of lithium intoxication, regardless of dosage or concomitant medications. This study encompasses a short duration (1 year), which is a limitation of this study. A longer research period would be desirable in future related studies.

In conclusion, this study indicated that serum lithium levels were not regularly measured in patients without dose changes and those prescribed lower doses. Notably, it may be considered inappropriate

TABLE 1 Characteristics of patients prescribed lithium for more than 60 days in the JMDC hospital-based database.

			Total *n*	Serum lithium concentration measured *n* (%)	Odds ratio	95% CI
Sex						
	Male		1318	577 (43.8)	Reference	
	Female		941	390 (41.4)	1.10	0.93–1.30
Age group (years)						
	<10		0			
	10–19		11	7 (63.6)	2.40	0.69–8.32
	20–29		92	41 (44.6)	1.10	0.70–1.74
	30–39		222	90 (40.5)	0.93	0.67–1.30
	40–49		398	168 (42.2)	Reference	
	50–59		531	234 (44.1)	1.08	0.83–1.40
	60–69		463	207 (44.7)	1.11	0.85–1.45
	70–79		401	174 (43.4)	1.05	0.79–1.39
	80–89		127	42 (33.1)	0.68	0.45–1.03
	≥90		14	4 (28.6)	0.55	0.17–1.78
Change in lithium dose						
	None		1947	770 (39.5)	Reference	
	Decrease only		118	65 (55.1)	1.88	1.29–2.73
	Increase only		129	85 (65.9)	2.95	2.03–4.30
	Increase and decrease		65	47 (72.3)	3.99	2.30–6.92
Daily dose of lithium (mg/day)						
	<200		38	9 (23.7)	0.54	0.25–1.15
	≥200, ≤400		1139	416 (36.5)	Reference	
	> 400, ≤800		984	489 (49.7)	1.72	1.44–2.04
	>800		98	53 (54.1)	2.05	1.35–3.10
Concomitant medications						
	ACE inhibitor/ARB 1	−	2097	890 (42.4)	Reference	
		+	162	77 (47.5)	1.23	0.89–1.69
	Diuretic	−	2214	944 (42.6)	Reference	
		+	45	23 (51.1)	1.41	0.78–2.54
	NSAID	−	1975	858 (43.4)	Reference	
		+	284	109 (38.4)	0.81	0.63–1.05

Note: Multiple logistic regression analysis was used for all analyses. Statistical analyses were performed with JMP pro, version 17.2 (SAS Institute Inc).
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; JMDC, JMDC Inc.; NSAID, nonsteroidal anti-inflammatory drug.

use if an AR, such as lithium intoxication, occurs in a patient in whom serum lithium levels were not regularly measured. Serum lithium concentrations should periodically be measured, even in patients without dose changes and those prescribed low doses.

AUTHOR CONTRIBUTIONS

Naohito Ide designed the study and wrote the manuscript. Naohito Ide and Ken-ichi Sako conducted data extraction and statistical analysis. Ken-ichi Sako interpreted the results and

contributed to the discussion. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data are within the paper.

ETHICS APPROVAL STATEMENT

N/A.

PATIENT CONSENT STATEMENT

N/A.

CLINICAL TRIAL REGISTRATION

N/A.

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