OPEN

Prevalence of Therapeutic Drug Monitoring for Lithium and the Impact of Regulatory Warnings: Analysis Using Japanese Claims Database

Nobuhiro Ooba, PhD, Daisuke Tsutsumi, MSc,* Naoko Kobayashi, PhD,* Shinji Hidaka, PhD,* Hiroyuki Hayashi, PhD,* Taku Obara, PhD,† Michihiro Satoh, PhD,‡ Kiyoshi Kubota, MD,§ and Noriyasu Fukuoka, PhD**

Background: Therapeutic drug monitoring (TDM) for lithium is recommended in guidelines; however, the prevalence of TDM for lithium is seldom reported. We have therefore investigated the prevalence of TDM for lithium and evaluated the impact of the regulatory warnings requiring routine TDM for lithium.

Methods: Monthly claims data covering around 1.7 million persons aged 20–74 years old during the period January 1, 2005, and March 31, 2015, were evaluated. All patients who had at least one prescription for lithium were selected and included to calculate the annual prevalence of TDM for lithium. Also we assessed whether the 2 regulatory warnings requiring routine TDM for lithium and issued in April 2012 and September 2012 had an impact on TDM for lithium, using segmented regression analysis.

Results: Between 2005 and 2014, 136,956 prescriptions of lithium were issued to 5823 patients, and the annual prevalence of TDM for lithium was 14.9% (95% confidence interval, 14.7%–15.1%). The analysis revealed that the mean prevalence increased abruptly by 6.9% ($P = 0.001$) after the regulatory warning in April 2012, whereas that the warning in September 2012 decreased by 1.2% ($P = 0.47$). There was no significant change in trends of period prevalence after the warning in April 2012 (April 2012–August 2012) compared with prevalence before the warning (April 2010–March 2012). Similarly, no significant change was observed in the trends before (April 2012–August 2012) and after (September 2012–March 2014) the subsequent warning in September 2012.

Conclusions: Results showed that the prevalence of TDM for lithium was low, although TDM for lithium was strongly recommended by the guidelines. Regulatory warnings requiring compliance with the measurement of blood levels during treatment with lithium, issued twice during the five-month period, were associated with an increase in the prevalence of TDM for lithium. However, the impact of the second warning was not remarkable compared with the first warning.

Key Words: lithium, prevalence, therapeutic drug monitoring, regulatory warning, segmented regression analysis

(*Ther Drug Monit* 2018;40:252–256)

INTRODUCTION

Therapeutic drug monitoring (TDM) is a useful tool for the management of individual patients receiving psychopharmacotherapy. Therapeutic drug monitoring is performed through the quantification of serum or plasma concentrations of medications for the purpose of dose optimization.[1] Therapeutic drug monitoring also enables dose adjustment, prevention of adverse drug reactions, and ascertainment of drug adherence, therapeutic nonresponse, or pharmacokinetic drug-drug interactions, as the concentration of the drug correlates with its clinical effect.[2] In psychiatric clinical practice, the benefits of using TDM for tricyclic antidepressants, antipsychotic drugs, and mood-stabilizing drugs have been reported.[3–5] Regarding mood-stabilizing drugs including lithium and typical antipsychotic drugs, TDM implementation is strongly recommended.[1] Therapeutic drug monitoring is likely to improve the safety of lithium because TDM has advantages in terms of reduced likelihood of toxicity or severe adverse effects.[6]

Lithium is widely used for the treatment of bipolar disorder.[7] Therapeutic drug monitoring for lithium has become standard because of lithium's narrow therapeutic range.[1,3] Measurements of its concentration at treatment initiation and during maintenance are recommended by therapeutic guidelines[5] and package inserts.[8] Reports on the prevalence of TDM for lithium are scarce even if nationwide surveys have sometimes been conducted in some

Received for publication September 8, 2017; accepted January 22, 2018.

From the *Nihon University School of Pharmacy, Funabashi, Chiba, Japan; †Department of Pharmaceutical Sciences, Tohoku University Hospital; ‡Division of Public Health, Hygiene and Epidemiology, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Miyagi, Japan; and §NPO Drug Safety Research Unit Japan, Bunkyo-ku, Tokyo, Japan.

Supported by JSPS KAKENHI Grant Number JP17K09134.

The authors declare no conflict of interest.

Correspondence: Nobuhiro Ooba, PhD, Nihon University School of Pharmacy, 7-7-1 Narashinodai, Funabashi, Chiba, 274-8555, Japan (e-mail: ooba.nobuhiro@nihon-u.ac.jp).

countries.[2,9,10] The prevalence of TDM for antipsychotics in Sweden was low (approximately 5%).[11] In Japan, when they received reports of cases of serious lithium poisoning and found that 52% of lithium users underwent no measurements of blood concentration of lithium at all, the Pharmaceuticals and Medical Devices Agency, a regulatory agency in Japan, issued a warning requiring the implementation of TDM for lithium in April 2012.[12] In September 2012, the Pharmaceuticals and Medical Devices Agency issued a second warning requiring more TDM for lithium.[13] In the warnings, cases of serious lithium poisoning were presented. According to the package insert for lithium,[8] serum lithium level should be measured about once a week at the initial phase of administration as well as during the dose-increase phase, until the maintenance dose is fixed. Then, it should be measured about once every 2 to 3 months during the maintenance dose phase. However, the clinical effect of regulatory warnings on TDM use for lithium has not been evaluated.

As Japanese claims contain codes related to TDM, it may be possible to estimate prevalence of TDM. The cost of TDM is reimbursed only for a limited number of drugs, including lithium. Even if multiple measurements of blood concentration of lithium were performed, the cost for only one TDM is reimbursed each month. As an exception, the cost for 2 TDMs per month is reimbursed if the patient uses 2 or more TDM drugs (eg, lithium and an antiepileptic drug).

The aim of this study was to estimate the prevalence of TDM for lithium and assess the impact of regulatory agency warnings on lithium prescribers.

MATERIALS AND METHODS

Data Sources

We used claims and enrollment data of the beneficiaries of dozens of corporate health insurance company policies in Japan. Data for 1,707,346 beneficiaries, who were workers in private firms, and their dependents aged between 20 and 74 years during the study period (January 1, 2005–March 31, 2014) were collected and maintained by Japan Medical Data Center Co, Ltd.[14] Information for demographics (age and sex), healthcare utilization (outpatient visits and hospitalization), drugs, diagnoses, and procedures, including orders for the measurement of blood concentration for TDM, was available from the claim data. In the claims data, more than 20,000 local drug codes are used to specify the trade name for all of the approved drugs.[15] Diagnoses were coded using the International Classification of Diseases, 10th edition (ICD-10). Enrollment data contained the dates of enrollment and disenrollment of the insured. The authors selected all patients prescribed lithium from the database and analyzed the data to find out the prevalence of TDM for lithium and to evaluate the impact of regulatory actions.

Statistical Analysis

We described the baseline characteristics of patients at the time of each patient's first lithium prescription. The numbers of lithium prescriptions and TDM measurements for lithium were counted by year. The annual prevalence of TDM for lithium in patients receiving the drug was calculated by dividing the number of claims with TDM for lithium by the number of patients with lithium. In addition, the prevalence was calculated in patients taking no TDM drugs (eg, valproic acid, carbamazepine, and haloperidol) other than lithium and in patients who did not have a lithium prescription in the previous 365 days (new lithium users).

In addition, the authors estimated the prevalence of TDM for lithium in each month between April 2010 and March 2014 and examined changes in the trend (slope) and level (intercept) of monthly prevalence before and after each of the 2 warnings. A segmented regression analysis[16] was applied to evaluate the impact of the regulatory warning issued in April and September 2012. The data for this analysis were restricted to the four-year period between April 2010 and March 2014, in which 2 warnings were issued in April and September 2012.

Moreover, we counted the number of patients with the ICD-10 code (T435) related to lithium intoxication and examined the implementation status of TDM. All analyses were performed using SAS V.9.4 (SAS Institute Inc, Cary, NC).

Ethical Considerations

This study was approved by the ethics committee at the Nihon University School of Pharmacy (No. 14-012). Obtaining informed consent was waived because the authors used only anonymized data with serial study IDs created by the data vendor.

RESULTS

Between January 2005 and March 2014, 136,956 prescriptions of lithium were issued to 5823 patients (Table 1). The proportion of patients with TDM performed at least once

TABLE 1. Characteristics of Patients Prescribed Lithium at Least Once

Duration	April 2005–March 2014
No. of prescriptions for lithium	136,956
No. of patients	5823
No. of patients with claims for TDM (%)	2830 (48.6)
Sex	
Male (%)	2965 (50.9)
Female (%)	2858 (49.1)
Mean age (SD)	39.6 (11.5)
Comorbidity (%)	
Bipolar affective disorder	1134 (19.5)
Sleep disorder	898 (15.4)
Depression	666 (11.4)
Schizophrenia	552 (9.5)
Comedication (%)	
Benzodiazepines	4670 (80.2)
Selective serotonin reuptake inhibitors	3212 (55.2)
Conventional antipsychotics	2320 (39.8)
Atypical antipsychotics	2203 (37.8)

during this period was 48.6%. The mean age of patients was 39.6 years and 2965 (50.9%) were men. The major diagnoses for those patients were bipolar affective disorder (19.5%), sleep disorder (15.4%), and depressive episode (11.4%). Concomitant medications included benzodiazepine (80.1%), selective serotonin reuptake inhibitor (55.2%), and conventional antipsychotics (39.8%).

Only 3 cases of lithium intoxication were observed; however, for one of them, the blood concentration for lithium was not measured until poisoning occurred.

The mean annual prevalence of TDM for lithium was 14.9% (95% confidence interval, 14.73%–15.11%), and the prevalence increased after 2012 (Table 2). By sex, the mean prevalence in women (14.6%, 14.34%–14.90%) and men (15.1%, 14.90%–15.41%) were almost the same ($P = 0.89$). Although the prevalence of TDM in new users of lithium (9.8%) was slightly higher ($P = 0.02$) than that in the prevalent users of lithium with or without other TDM drugs (8.9%), the prevalence in users of lithium without other TDM drugs (7.3%) was lower ($P < 0.01$) than those of either of the 2 populations.

In Figure 1, the observed monthly prevalence (solid line) and the prevalence estimated by the segmented regression analysis (dotted line) are shown. The estimated mean level (intercept) of the prevalence jumped abruptly by 6.9% ($P = 0.001$) after the regulatory warning in April 2012, whereas no change in the level was observed after the warning in September 2012 ($P = 0.47$). Compared with the trend (slope) of the prevalence during the period from April 2010 to March 2012, before the first warning in April 2012, there was no significant change in the trend during the postwarning period from April 2012–August 2012, after the warning. Similarly, no significant change in the trend was observed between 2 periods before (April 2012–August 2012) and after (September 2012–March 2014) the second warning in September 2012.

DISCUSSION

We described the annual prevalence of TDM use in patients prescribed lithium in a young- and middle-aged Japanese population between January 2005 and March 2014, which was approximately 15%, although the prevalence in new patients was slightly lower in new users (9.8%). These figures were almost completely consistent throughout the study period. Measurement of blood concentration of lithium in patients prescribed that the drug is recommended in the package insert[8] and guidelines;[5] however, the frequency of TDM for lithium users was low. Regulatory warnings[12,13] requiring compliance with the measurement of blood levels during treatment with lithium, issued twice during the five-month period, were associated with an increase in the prevalence of TDM for lithium. However, the impact of the second warning was not remarkable compared with the first one in the segmented regression analysis.[16]

The annual prevalence (14.9%) in the Japanese patients seemed to be low in this study; a low prevalence (approximately 2%–5%) of TDM for antipsychotics was also shown in a previous study.[11] It has been recognized by psychiatric physicians that only a relatively small proportion of lithium-treated patients are free of adverse drug reactions.[17] Lithium toxicity is preventable in most cases, primarily by careful clinical examination but also by the proper use of TDM. In managing the side effects of lithium, one of the basic strategies is watchful waiting[17] along with the judicious use of TDM.

In addition, the prevalence of men receiving TDM was higher than that of women in a previous study on antipsychotics,[11] which is contrary to findings of Marcus et al.[18] Our findings showed that the prevalence of women receiving TDM was similar to that of men, although the reason of this is unknown.

Some types of warnings were shown to have minimum impact on clinical practice. When cisapride, a drug metabolized by the cytochrome P450 3A4 (CYP 3A4) enzyme, was simultaneously used by patients taking an inhibitor drug for CYP 3A4, the risk of serious cardiac arrhythmias was increased.[19] Although 3 regulatory warnings were issued for cisapride, Smalley et al[20] reported that these actions had no impact on the contraindicated use of cisapride, consequently. In our study using the segmented regression analysis, the first warning was associated with an increase of the prevalence of

TABLE 2. The Number of Prescriptions and Measurements of Blood Concentration for Lithium, by Year

	With at Least One Prescription for Lithium		Without Other TDM Drugs Except for Lithium		New Lithium Users	
Year	No. of Prescriptions	No. of Claims for TDM (%)	No. of Prescription	No. Claims for TDM (%)	No. Prescriptions	No. Claims for TDM (%)
2005	3435	350 (10.19)	2562	157 (6.13)	—	—
2006	3803	370 (9.73)	2868	192 (6.69)	763	122 (15.99)
2007	4395	512 (11.65)	3183	216 (6.79)	1737	190 (10.94)
2008	7559	903 (11.95)	5633	391 (7.31)	2363	286 (12.10)
2009	11,890	1452 (12.21)	9274	678 (7.15)	3716	377 (10.15)
2010	18,133	2258 (12.45)	14,376	1028 (7.05)	5658	545 (9.63)
2011	22,152	2873 (12.97)	17,569	1239 (7.65)	8343	842 (10.09)
2012	31,994	5531 (17.29)	24,919	1906 (7.36)	12,204	1201 (9.84)
2013	27,801	5206 (18.73)	22,029	1621 (7.65)	13,001	1121 (8.62)
2014*	5794	980 (16.91)	4811	368 (7.27)	2730	246 (9.01)

*From January 2014–March 2014.

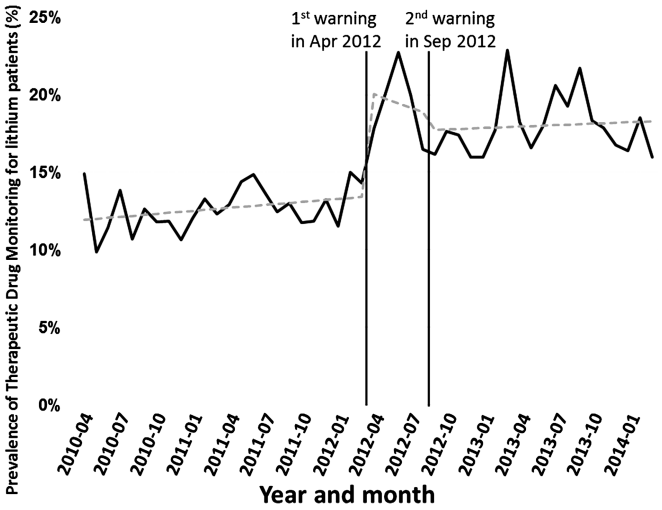

FIGURE 1. Prevalence of TDM for lithium patients (%). Monthly prevalence (black solid line) and the regression line (dotted gray line) estimated by the segmented regression analysis are shown. The regulatory warnings were issued in April 2012 and September 2012, respectively.

TDM for lithium, although the second warning had no significant impact. To enhance TDM of lithium, intervention at the national or hospital level in addition to warnings may be useful. To confirm implementation of TDM, for example, it may be necessary to establish registration for patients prescribed lithium, to complement "regulatory warnings." In addition, additional risk communication such as direct communication from a pharmacist to a physician in each hospital may be necessary because there was a report showing that pharmacist intervention was effective for TDM use.[21]

The second regulatory warning did not show an immediate effect in our study. The effect of the second warning was also different from the first one in various studies[22,23] of cisapride. These findings may be due to different research designs and analysis methods. It was also possible that several intermediate mechanisms (warnings inside the hospitals or professional bodies and sharing the information between prescribers etc.) after the second warning were different from those after the first warning.

The strength of the current study is that we estimated the prevalence of TDM for lithium. Although related research has included a nationwide study of TDM of lithium,[2,9,10,24–26] only a few studies have evaluated the prevalence of TDM. To estimate prevalence, data are required on both the population prescribed lithium (total population) and the population in which TDM for lithium was performed. The prevalence of TDM for lithium was assessed in several countries as 0.13% (UK in 1992),[27] 1.2% (Germany in 2006),[28] 8.9% (Japan: our study), 30% (UK in 2010),[29] 36.5% (US in 1999),[18] and 80% (UK in 2017).[30] Therapeutic drug monitoring for lithium in the United States and Japan is underused, whereas the increase in prevalence in the UK may be related to support by the National Patient Safety Agency.[31]

This study has some limitations. First, the authors measured the prevalence of TDM for lithium but could not measure the incidence of lithium toxicity. Second, the authors did not have accurate information on the number of tests to measure blood concentration of lithium. Instead of directly counting the number of TDM measurements for lithium, we counted the number of healthcare claims indicating that blood concentrations were examined. Because TDM for lithium can be claimed only once a month, we might have underestimated the prevalence of TDM for lithium. Third, by the claims data with TDM, the authors were unable to identify which TDM-targeted drug was measured. However, the prevalence of TDM in patients who had not been prescribed TDM drugs other than lithium (7.3%) was lower than that of lithium users with or without other TDM drugs (14.9%). Fourth, these findings might not be generalizable to the elderly population and people under the age of 20 because the study population included only patients between 20 and 74 years old. However, as the prevalence of TDM for antipsychotics was highest in the young- and middle-aged population, according to Wallerstedt and Lindh,[11] and if this was also the case with our study, the prevalence in the children or elderly population might be less than 14.9%. Fifth, the authors could not distinguish patients between those in psychiatric special hospitals and those in other hospitals. According to the study using the retrospective chart review of inpatients using lithium in a psychiatric hospital, 73% of lithium users underwent blood concentration measurement.[32] The prevalence may be therefore different depending on hospital characteristics, such as general hospitals versus university hospitals or psychiatric specialty hospitals.

CONCLUSIONS

We found that the annual prevalence of TDM for lithium was low (approximately 15%), although TDM for lithium is strongly recommended by the guidelines and package inserts for lithium. Findings indicate that TDM is not a standard in clinical practice. The regulatory warnings had a small impact in raising the prevalence of TDM for lithium. To improve safety for lithium users and to learn the prevalence of TDM in pediatric and elderly populations, further study is needed.

REFERENCES

1. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry.* 2011;44:195–235.
2. Guo W, Guo GX, Sun C, et al. Therapeutic drug monitoring of psychotropic drugs in China: a nationwide survey. *Ther Drug Monit.* 2013;35:816–822.
3. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach. Part II: clinical pharmacology and therapeutic monitoring. *CNS Drugs.* 2009;23:331–349.
4. Radziwoń-Zaleska M, Matsumoto H, Skalski M, et al. Therapeutic tricyclic antidepressant drug monitoring in younger and older depressive patients. *Pharmacol Rep.* 2006;58:501–506.
5. Kanba S, Kato T, Terao T, et al. Guideline for treatment of bipolar disorder by the Japanese society of mood disorders, 2012. *Psychiatry Clin Neurosci.* 2013;67:285–300.
6. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol.* 2001;52:45S–54S.
7. Fountoulakis KN, Yatham L, Grunze H, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar

disorder in adults (CINP-BD-2017), Part 2: review, grading of the evidence, and a precise algorithm. *Int J Neuropsychopharmacol.* 2017;20:121–179.
8. Lithium [package insert] (In Japanese). Available at: http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400059_1179017F1056_1_12. Accessed August 25, 2017.
9. Conca A, Schmidt E, Pastore M, et al. Therapeutic drug monitoring in Italian psychiatry. *Pharmacopsychiatry*. 2011;44:259–262.
10. Morris RG. Delivery of therapeutic drug monitoring services: survey of Australasian clinical pharmacology laboratories. *Ther Drug Monit.* 1998;20:598–601.
11. Wallerstedt SM, Lindh JD. Prevalence of therapeutic drug monitoring for antidepressants and antipsychotics in stockholm, Sweden: a longitudinal analysis. *Ther Drug Monit.* 2015;37:461–465.
12. Regulatory warning on lithium at April 2012 [in Japanese]. Available at: https://www.thpa.or.jp/sites/default/files/pdf/tekisei_pmda_07.pdf. Accessed August 25, 2017.
13. Pharmaceuticals and Medical Devices Agency. Compliance with measurement of blood lithium level during treatment with lithium carbonate. In: *PMDA Alert for Proper Use of Drugs*. 2012. Available at: https://www.pmda.go.jp/files/000153187.pdf. Accessed August 25, 2017.
14. Kimura S, Sato T, Ikeda S, et al. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. *J Epidemiol.* 2010;20:413–419.
15. Ministry of Health, Labour and Welfare. National Health Insurance drug list. Available at: http://apps.who.int/medicinedocs/en/d/Js19548ja/. Accessed August 25, 2017.
16. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther.* 2002;27:299–309.
17. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord.* 2016;4:27.
18. Marcus SC, Olfson M, Pincus HA, et al. Therapeutic drug monitoring of mood stabilizers in Medicaid patients with bipolar disorder. *Am J Psychiatry*. 1999;156:1014–1018.
19. Enger C, Cali C, Walker AM. Serious ventricular arrhythmias among users of cisapride and other QT-prolonging agents in the United States. *Pharmacoepidemiol Drug Saf.* 2002;11:477–546.
20. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of food and drug administration regulatory action. *JAMA*. 2000;284:3036–3039.
21. Ratanajamit C, Kaewpibal P, Setthawacharavanich S, et al. Effect of pharmacist participation in the health care team on therapeutic drug monitoring utilization for antiepileptic drugs. *J Med Assoc Thai.* 2009;92:1500–1507.
22. Guo JJ, Curkendall S, Jones JK, et al. Impact of cisapride label changes on codispensing of contraindicated medications. *Pharmacoepidemiol Drug Saf.* 2003;12:295–301.
23. Weatherby LB, Nordstrom BL, Fife D, et al. The impact of wording in "Dear doctor" letters and in black box labels. *Clin Pharmacol Ther.* 2002;72:735–742.
24. Amdisen A. Serum concentration and clinical supervision in monitoring of lithium treatment. *Ther Drug Monit.* 1980;2:73–83.
25. Eryılmaz G, Hızlı Sayar G, Gül IG, et al. Therapeutic drug monitoring: perspectives of psychiatrists in Turkey. *Int J Psychiatry Clin Pract.* 2015;19:60–64.
26. Karki SD, Holden JM. Appropriateness of the use of serum lithium assays. *Drug Intell Clin Pharm.* 1988;22:151–153.
27. Kehoe RF, Mander AJ. Lithium treatment: prescribing and monitoring habits in hospital and general practice. *BMJ*. 1992;304:552–554.
28. Mann K, Hiemke C, Lotz J, et al. Appropriateness of plasma level determinations for lithium and valproate in routine care of psychiatric inpatients with affective disorders. *J Clin Psychopharmacol.* 2006;26:671–673.
29. Collins N, Barnes TR, Shingleton-Smith A, et al. Standards of lithium monitoring in mental health trusts in the UK. *BMC Psychiatry*. 2010;10:80.
30. Savage N, Green J, Seshadri M, et al. Study on lithium monitoring amongst patients in a community mental health and primary care setting in rural England. *Psychiatr Danub.* 2017;29:481–486.
31. Paton C, Adroer R, Barnes TR. Monitoring lithium therapy: the impact of a quality improvement programme in the UK. *Bipolar Disord.* 2013;15:865–875.
32. Ratanajamit C, Soorapan S, Doang-ngern T, et al. Appropriateness of therapeutic drug monitoring for lithium. *J Med Assoc Thai*. 2006;89:1954–1960.