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MICRO REPORT

Effect of antipsychotics on serum lithium levels and white blood cell counts

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Abstract

Lithium carbonate is used to increase white blood cell counts as a means of counteracting leukopenia caused by the administration of antipsychotic drugs. To evaluate the effect of antipsychotics on the leukocyte-enhancing effect of lithium, we compared white blood cell counts, serum lithium levels, and lithium dosage in patients receiving antipsychotics and lithium in combination and patients receiving lithium alone. Chlorpromazine equivalent values were used as an indicator of the antipsychotic dose.

Lithium serum levels were measured in 41 hospitalized patients. The lithium dose in the combination group (median, 800 mg) was significantly higher than that in group receiving only lithium (median, 400 mg) ($P = 0.03$). The lithium doses in the combination group receiving ≥1000 mg chlorpromazine equivalents (overdosing; median lithium dose 800 mg) and the combination group treated with 600-999 mg chlorpromazine equivalents (high dosing; median lithium dose 800 mg) were significantly higher than the group that was not treated with antipsychotic medication, with median lithium dose 400 mg ($P < 0.05$).There were no significant differences in the white blood cell counts and serum lithium levels.

Because of the large variety of antipsychotic drugs used in combination with lithium and the various doses used, it was difficult to evaluate the effects of lithium, with or without antipsychotic administration, on leukocyte count enhancement. We are planning to study a larger number of patients and, since renal function could not be assessed in this study, we will also focus on renal function, including urine output.

KEYWORDS

Antipsychotics, chlorpromazine equivalents, leukopenia, lithium carbonate, white blood cell count

1 | INTRODUCTION

Lithium carbonate (Li_2CO_3), a treatment for manic states of manic and manic-depressive illnesses,[1] is known to have leukocytosis as a side effect. As a result of the ability of Li_2CO_3 to induce leukocytosis, patients[2-6] who develop drug-induced leukopenia due to administration of antipsychotics (APs) may receive Li_2CO_3 for therapeutic purposes. The Guidelines for Drug Treatment of Schizophrenia[7] state that if a patient taking clozapine develops leukopenia, "we recommend lithium weekly as a pharmacotherapy."

Previous retrospective studies in humans have shown a positive association between white blood cell (WBC) count and Li_2CO_3 dose (Li-dose) in treated patients.[8, 9] However, a consensus on the relationship between WBC count and serum Li levels (Li-concn) has not been reached.[9-11]

Therefore, in this study, in an effort to evaluate the effect of APs on the leukocyte-enhancing effect of lithium, we investigated WBC count, Li-dose, and Li-concn in patients receiving Li_2CO_3 and AP in combination, and compared these values with those of patients receiving Li_2CO_3 alone. Then, chlorpromazine equivalent (Cp) values[12] were used as an indicator of the dosage of APs, and the association between Cp values and WBC count was evaluated.

2 | METHODS

2.1 | Participants

The participants were patients whose Li-concn was measured at the Hospital Bando between February 4, 2014, and March 9, 2017.

2.2 | Serum lithium concentrations

Li-concn was measured using the electrode method (Ion Selectivity Analyzer Rapidkem 754, Siemens Healthcare Diagnostics Co., Ltd., Tokyo Metropolitan). Samples that met the following exclusion criteria were excluded: samples collected from patients who were under conditions affecting WBC counts, undergoing treatment of infection, undergoing treatment with cancer chemotherapy, undergoing nonsteroidal anti-inflammatory or analgesic combination therapy, or vaccinated against various infectious diseases; had poor compliance or hyperlithemia due to sodium deficiency (refusal to eat); blood samples collected from patients within 7 days of Li_2CO_3 dose change; blood samples collected from patients within 14 days of AP dose change; and blood samples collected from patients whose Li_2CO_3 dose could not be determined.

When more than one blood sample was taken from the same patient and more than one Li-concn was measured, the measurement with the highest Li-concn was used for analysis, using a previous report[13] as a reference.

2.3 | Cp value

Cp values are calculated such that 300-600 mg is considered adequate dosing, 600 mg-999 mg is considered high dosing, and 1000 mg or more is considered overdosing.[14, 15] Therefore, in this study, the group of patients whose Cp values were less than the adequate dose (1-299 mg) were classified as the low-dose group (Cp/Lo). The group of patients whose Cp values were in the adequate dose range (300-599 mg) were classified as the appropriate dose group [(Cp/Ap)], the group of patients whose Cp values were in the high-dose range (600-999 mg) were classified as the high-dose group [(Cp/Hi)] and the group of patients whose Cp values fell into the overdose range (≥1000 mg) were classified as the overdose group (Cp/Ov).

Patients who did not receive AP were classified as the non-AP group.

2.4 | Statistical analysis

For statistical analysis, we used IBM SPSS Statistics Ver 25 (Japan IRB, Inc, Tokyo Metropolitan Area).

Li-dose and Li-concn correlations, WBC count and Li-dose correlations, and WBC count and Li-concn correlations were examined using Spearman's rank correlation. To examine the effects of the presence/absence of AP dosage on Li-dose, Li-concn, and WBC count, the Mann–Whitney test was used. Finally, to examine the effects of Cp on Li-dose, Li-concn and WBC count, the Shirley–Williams test was used. A p-value of less than 0.05 was judged to be statistically significant.

3 | RESULTS

3.1 | Participants

Li-concn was measured in 53 patients and after application of the exclusion criteria, 41 patients were included in the survey. Excluded patients comprised one patient with poor compliance, three patients refusing to eat, three patients who were within 7 days of Li_2CO_3 dose change or within 14 days of AP dose change, and five patients for whom the Li_2CO_3 dose could not be determined.

The median (range) Li-dose was 600 mg/day (200-1200 mg/ day) and Li-concn was 0.79 mEq/L (0.20-1.30 mEq/L).

Of the 41 patients included, 34 (82.9%) were receiving concomitant AP therapy (atypical antipsychotics, 7; typical antipsychotics, 2); the Cp/Hi group had the most individuals receiving concomitant AP therapy, with 13 (38.2%, Table 1). The median (range) Cp value was 600 mg/day (range, 38-2356 mg/day).

3.2 | Correlations between WBC count and Li-dose, WBC count and Li-concn, Li-dose and Li-concn

There was a weak positive association between WBC count and Li-dose in the 41 included subjects, but the differences were not significant (Spearman's rs = 0.29, $P = 0.07$). In contrast, no correlations were observed between WBC count and Li-concn (Spearman rs = 0.12, $P = 0.47$). There was a weak positive correlation between Li-dose and Li-concn, but the difference was not significant (Spearman rs = 0.30, $P = 0.06$).

TABLE 1 Characteristic of patients

		n	(%)
Total patients		41	(100.0%)
Gender			
Male		23	(56.1%)
Female		18	(43.9%)
Median age in years (range)		53 (18-82)	
Patients not receiving antipsychotics		7	(17.1%)
Patients who received antipsychotics		34	(82.9%)
Patient group	(Chlorpromazine equivalent dose)	34	(100.0%)
Low dose group	(1-299 mg/d)	8	(23.5%)
Appropriated dose group	(300-599 mg/d)	6	(17.6%)
High dose group	(600-999 mg/d)	13	(38.2%)
Over dose group	(>1000 mg/d)	7	(20.6%)
Cumulative total number of patients who received atypical antipsychotics		48	(100%)
Olanzapine		13	(27.1%)
Aripiprazole		12	(25.0%)
Risperidone		10	(20.8%)
Quetiapine		5	(10.4%)
Zotepine		4	(8.3%)
Paliperidone		3	(6.3%)
Blonanserin		1	(2.1%)
Cumulative total number of patients who received typical antipsychotics		2	(100%)
Haloperidol		1	(50.0%)
Chlorpromazine		1	(50.0%)

3.3 | Effects of AP-administration on Li-dose, Li-concn, and WBC count

The Li-dose in the AP-treated group was significantly higher than that in the non-AP group (median, 800 *v* 400 mg, $P = 0.03$) (Figure 1).

There were no significant differences in Li-concn (median; 0.80 *v* 0.71 mEq/L, $P = 0.24$) and WBC count (median; 6155 *v* 6760 cells per mm^3, $P = 0.13$) in the AP and non-AP groups.

3.4 | Effects of Cp values on Li-dose, Li-concn, and WBC count

The Li-dose in the Cp/Hi group was significantly higher than that in the non-AP group (median, 800 *v* 400 mg, $P < 0.05$). Similarly, the Li-dose in the Cp/Ov group was significantly higher than that in the non-AP group (median, 800 *v* 400 mg, $P < 0.05$) (Figure 2A). The Li-concn and WBC counts in the non-AP group were not significantly different from those in the AP group (Figure 2B,C).

4 | DISCUSSION

This study found a weak positive association ($P = 0.07$) between Li-dose and WBC count, similar to previous retrospective studies in humans.[8, 9] These results suggest that Li_2CO_3 may contribute to the increase in WBC count in a dose-dependent manner.

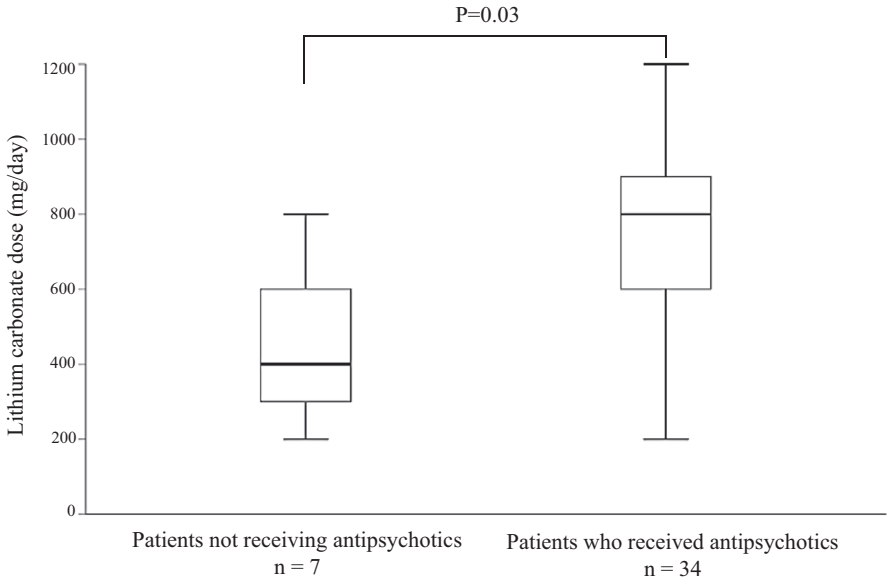

FIGURE 1 Effects of antipsychotics on lithium carbonate dose

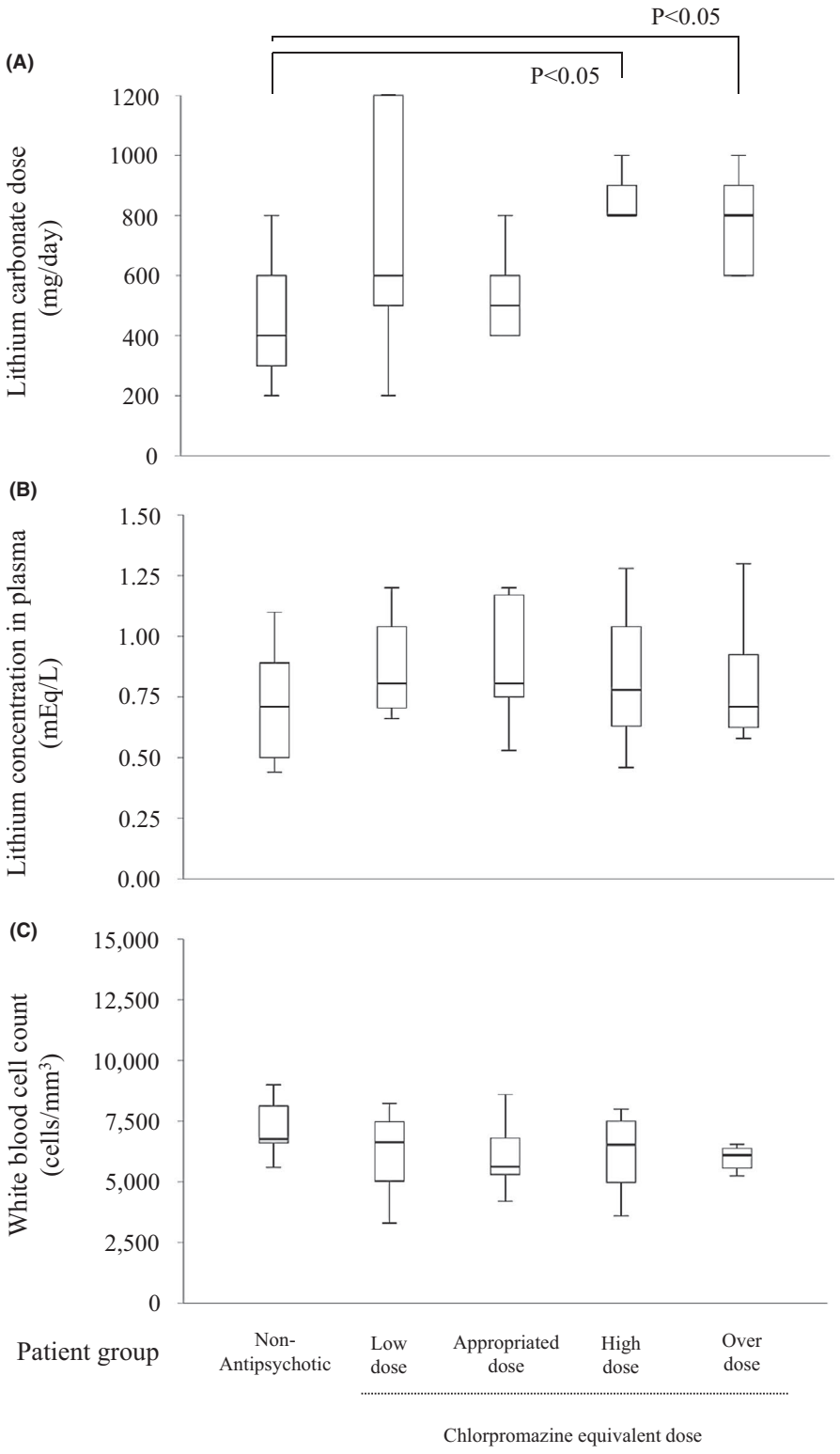

FIGURE 2 Effect of chlorpromazine equivalent dose on lithium carbonate dose, serum lithium concentration, and white blood cell count. A, Effect of chlorpromazine equivalent dose on lithium carbonate dose. B, Effect of chlorpromazine equivalent dose on serum lithium concentration. C, Effect of chlorpromazine equivalent dose on white blood cell count

We found no correlation between Li-concn and WBC count, similar to previous reports[9-11] in humans. Li-concn has a very narrow therapeutic efficacy range of 0.6-1.2mEq/L (trough levels).[1] Therefore, we are currently investigating the association between long-term Li-concn and WBC count in patients whose Li-concn is maintained at the upper therapeutic window.

A side effect of AP drugs is the anticholinergic effect. Reports have suggested that this anticholinergic effect may cause decreased urine output and delayed elimination of lithium, possibly increasing Li-concn.[13, 16] In the present study, there were no differences in Li-concn between the two groups, even though the Li- dose in the AP group was significantly higher than that in the

non-AP group. Physiological factors that can suppress increases in Li-concn include inhibition of lithium absorption from the digestive tract, promotion of lithium excretion in the urine, and inhibition of lithium reabsorption in the kidney. Therefore, we are currently considering analyses focused on renal function, including urine output.

A retrospective study of patients treated with Li_2CO_3 and AP reported higher levels of Li-concn in patients treated with Li_2CO_3 and AP than in patients treated with Li_2CO_3 alone.[13] Of the 59 patients who received AP, 43 (73%) received quetiapine. Hence, a reason for the increased Li-concn in the combination group was the bias of the administered APs toward quetiapine. Another report found that Li-concn may be elevated in a variety of situations, including increased Cp values, increased numbers of concomitant APs, and concurrent use of zotepine and olanzapine.[16] In a clinical study of risperidone tablets, it was reported that the pharmacokinetics of lithium in patients receiving Li_2CO_3 in combination with APs other than risperidone was not affected when their prescriptions were changed to a combination of risperidone and Li_2CO_3 (Demling 1997, unpublished data).[17] Because of the large number of APs used in combination with Li_2CO_3 and the variety of AP doses used in our study, we are currently investigating the effects of different AP drugs and AP dosages on Li-concn in an increased number of patients.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study was approved by the ethics committee of the Hospital Bando (approval number 201904002).

INFORMED CONSENT

Informed consent was obtained via an opt-out form in-hospital bulletin board.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Approval number 201904002.

ANIMAL STUDIES

Not applicable.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Study concepts and design: Ryo Obara, Takashi Tomita, and Yukinao Kohda. Data collection: Ryo Obara, akashi Tomita, Hidekazu Goto, Yukinao Kohda, Tadashi Yoshida. Analysis and interpretation of data: Ryo Obara, Takashi Tomita. Writing papers: Ryo Obara, Takashi Tomita. Important revisions to the paper: Yukinao Kohda and Kenzo Kudo. Approval of the final draft: Ryo Obara, Takashi Tomita, Hidekazu Goto, Yukinao Kohda, Tadashi Yoshida, Kenzo Kudo.

DATA AVAILABILITY STATEMENT

No additional information is available for this paper. All data generated or analyzed during this study are included in this article.

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