Relationship between Patients' Clinical Background and Lithium Concentration in Plasma : An Analysis of TDM Database in a University Hospital in Japan

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The purpose of the present study was to clarify the relationship between Japanese patients' clinical background and the lithium concentration in plasma. We extracted patient data for 4 years from our database (April 1, 1993 through March 30, 1997) in the Clinical Pharmacology Center of Oita Medical University Hospital, under the conditions that 1) the patient's body weight, sex and age were known, 2) the patient's lithium concentration in plasma was confirmed to be in steady state at more than 30 days after initial drug administration, and 3) the sample was taken at trough level at exactly 12 hours after the previous drug intake. Sixty-four out of 752 samples met the criteria. The ratios of the lithium concentration in plasma to the dose per kilogram body weight (C/D ratio) were compared according to the patients' background factors ; 1) in/outpatient status and 2) age. The mean C/D ratio of inpatients was higher than that of outpatients. The C/D ratio increased with age, and it tended to increase more in inpatients. The correlation of the concentration to the dose was higher with the higher age. We propose by analyzing the patients' C/D ratios, that the patient's clinical background correlates with the patient's drug compliance, or pharmacokinetics. The C/D ratio may be a useful indicator to evaluate the patient's drug compliance and pharmacokinetics in daily bedside therapeutic drug monitoring.

Key words : lithium, therapeutic drug monitoring (TDM), compliance, pharmacokinetics

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Introduction

Therapeutic plasma concentrations have been established for lithium¹⁻³⁾, which is a drug widely used against affective disorders and other psychiatric diseases. The plasma lithium concentration is often monitored in the daily medical practice because of its narrow therapeutic range. The dose of the drug is often limited because of its high toxicity. Subtherapeutic or toxic plasma concentrations of psychotropic agents can result from standard doses because of a large interindividual variability of drug metabolism or excretion⁴⁻⁶⁾. Maximizing efficacy and preventing toxicity is the goal of the rational drug therapy, and therapeutic drug monitoring (TDM) is a useful tool for physicians to optimize the dosage. However, it may sometimes be difficult to evaluate unexpected drug concentrations especially when only a limited number of samples are available. Clinicians want to know the relationship between each patient's clinical background and the observed drug concentration to individualize the regimen of drug therapy. Applying population pharmacokinetics for every patient is not always practical due to the limitation of analytical utilities both in time and space. It may be recommended to simplify routine TDM by using a simpler tool.

In Oita Medical University, TDM has been widely applied for numerous drugs including lithium. All data of TDM are stored in the computer database at Clinical Pharmacology Center, and evaluation is made by clinical pharmacologists and pharmacists. The purpose of the present study was to overview our TDM database for lithium and to clarify the relationship between patients' clinical background and the trough lithium concentration at steady state by looking at the ratios of the lithium concen-

tration in plasma to the dose per kilogram body weight (C/D ratio), which might be a useful tool for routine TDM for drugs with a linear correlation between the dose and the concentration.

Materials and Methods

We extracted patient data for 4 years from our database (April 1, 1993 through March 30, 1997) in the Clinical Pharmacology Center of Oita Medical University Hospital, under the conditions that 1) the patient's lithium dose (mg), body weight (kg), sex and age were known, 2) the patient's lithium concentration in plasma (mEq/L) was confirmed to be in steady state at more than 30 days after initial drug administration, and 3) the sample was taken at trough level at exactly 12 hours after the previous drug intake. Lithium concentrations were measured using a flame photometer (Hitachi 775-A) during the described period. Sixty-four out of 752 samples met the criteria. The ratio of the lithium concentration in plasma (mEq/L) to the dose per kilogram body weight (mg/kg-BW) (C/D ratio) was compared to the patient's background factors; 1) in/outpatient status and 2) age. Pearson's correlation coefficient values were calculated to clarify the relationship between the dose and the lithium concentration in plasma, and factorial analysis of variance (ANOVA) and χ square test were used for statistical analyses. A p value less than 5% was considered to be statistically significant.

Results

Table 1 shows patients' characteristics according to in/outpatient status, and Table 2 according to age groups; less than 35 (younger), between 35 and 50 (middle aged), and over 50 years old (elderly). No significant

Table 1 Patients' Characteristics According to In/Outpatient Status

	Inpatients (n=33)	Outpatients (n=30)	p value
Age	36.7±14.7	39.8±11.0	n. s.
Body weight (kg)	58.3±10.5	58.9±15.5	n. s.
Dose/kg body weight (mg/kg)	15.0±6.0	16.3±5.2	n. s.
Male/Female	15/18	6/24	n. s.
Lithium concentration (mEq/L)	0.70±0.17	0.62±0.17	n. s.

Data are shown as mean±S. D. and ratio in number.

n. s. : not significant

Table 2 Patients' Characteristics According to Age Group

	<35 years old (n=25)	35~50 years old (n=22)	50 years old < (n=16)	p value
Age	24.3±4.5	41.8±4.1	54.8±3.9	
Body weight (kg)	59.9±13.4	58.6±15.0	56.5±8.6	n. s.
Dose/kg (mg/kg)	18.1±6.1	15.1±5.4	12.8±3.1	p<0.01
Male/Female	5/20	7/15	9/7	n. s.
In/Outpatient	16/9	7/15	10/6	n. s.
Lithium concentration (mEq/L)	0.66±0.19	0.65±0.19	0.68±0.14	n. s.

Data are shown as mean±S. D. and ratio in number.

n. s. : not significant

difference in age, body weight, dose of lithium, sex ratio, or lithium concentration was found between inpatient and outpatient groups. However, the mean lithium concentration in inpatients tended to be higher than that in outpatients ($0.01 < p < 0.05$). A significant difference was found in the dose of lithium among the age groups ($p < 0.01$). However, no significant difference was found in age, body weight, sex ratio, in/outpatient ratio, or lithium concentration among the age groups.

The mean C/D ratio of inpatients was significantly higher than that of outpatients ($p < 0.01$) (Fig. 1). The C/D ratio was significantly increased with age ($p < 0.01$) (Fig. 2), and it tended to increase more in inpatients (Fig. 3). One-way factorial analysis followed by post hoc test (Bonferoni/Dunn test) revealed statistical differences of the mean C/D ratios among the

age groups in inpatients (younger v. s. middle aged group : $p < 0.05$, younger v. s. elderly : $p < 0.01$). There was a significant difference of the mean C/D ratios between inpatients and outpatients in the middle aged group ($p < 0.05$) and in the elderly group ($p < 0.01$) (Fig. 3). The C/D ratio became greater with higher age, although the correlation between the concentration and the dose tended to be smaller (Fig. 4). The correlation coefficient values became smaller as age increased ; $r = 0.701$ ($p < 0.01$) for the younger group, $r = 0.529$ ($p < 0.05$) for the middle aged group, and $r = 0.326$ for the elderly group.

Discussion

Despite the regular prescription schedule, physicians may experience some cases that show unexpected changes in their lithium con-

Fig. 1 The C/D ratios according to inpatient and outpatient status. The mean C/D ratio of inpatients was significantly higher than that of outpatients ($p < 0.01$). Significant difference by factorial analysis of variance (2×3 ANOVA) is shown by p value. All data are shown as mean $\pm$ S. D.

Fig. 2 The C/D ratios according to age groups. The C/D ratio significantly increased with age ($p < 0.01$). Significant difference by factorial analysis of variance (2×3 ANOVA) is shown by p value. All data are shown as mean $\pm$ S. D.

Fig. 3 The C/D ratios according to age groups. The C/D ratio significantly increased with age ($p < 0.01$). Significant difference by factorial analysis of variance (one-way ANOVA) is shown by p value. Significant differences by multiple comparison (Bonferroni/Dunn test) are shown by asterisks (* $p < 0.05$, ** $p < 0.01$). All data are shown as mean $\pm$ S. D.

Fig. 4 Relationship between dose (mg/kg) and lithium concentrations in different age groups. The lithium concentration to the dose was higher with higher age. However, the correlation coefficient became less as age increased; $r = 0.701$ ($p < 0.01$) for the younger group, $r = 0.529$ ($p < 0.05$) for the middle aged group, and $r = 0.326$ for the elderly group.

centration in the regular follow-ups, especially after patients were discharged from in-hospital care during which their lithium concentrations in plasma had been steadily maintained. In addition, in elderly patients, the lithium concentration may easily elevate, and prediction of their concentration is difficult^{2,7)}. Patients in outpatient status are generally believed to show lower drug compliance than those in inpatient status⁸⁾, and elderly patients may have impaired renal elimination with age^{2,7,9)}. These are partly why TDM has become so popular for individualization in drug therapy in a daily psychiatric practice.

In the present study, patients' data were extracted from a TDM database of a Japanese university hospital to clarify the relationship between patients' clinical background and lithium concentration in plasma. Sixty-four out of 752 samples over 4 years (April 1, 1993 through March 30, 1997) met the extraction criteria : 1) the patient's lithium dose (mg), body weight (kg), sex and age were known, 2) the patient's lithium concentration in plasma (mEq/L) was confirmed to be in steady state at more than 30 days after initial drug administration, and 3) the sample was taken at trough level exactly at 12 hours after the previous drug intake. Each criterion interacted so greatly as to limit the samples, however, our analysis showed a clear data tendency.

The relationship between patients' clinical background such as in/outpatient status and age on lithium concentrations in plasma has been examined by using C/D ratio. The mean C/D ratio was greater in inpatients than in outpatients. This difference was compatible for the hypothesis that drug compliance in outpatients is lower than that in inpatients, although it could also be explained by between-group characteristic difference, if any, in renal

function, coadministered drugs, and so on, which were not examined in this study. The elevation of C/D ratios was observed in the elderly, which was possibly explainable by the impaired renal clearance with age. In the elderly, the relationship between the dose and lithium concentration was smaller. Further study may be needed to investigate if it is due to the great interindividual variability of lithium pharmacokinetics in the elderly or lower drug compliance in some population of the patients. A recent survey performed by our group in Japan showed that drug compliance in the elderly is better than that in the young patients¹⁰⁾. However, this report limited the patient population by selecting them only from out patients clinics of internal medicine at a university hospital. In the present study, we showed the increase in C/D ratio with age, which may not have been revealed if drug compliance in the elderly was extremely poor. Patients in this study may have a better physician-patient relationship and a higher tolerance because they had been successfully treated in a university hospital at least for 30 days, so we may have to carefully generalize the study results.

There has been a widespread application of population pharmacokinetic parameter estimation such as the Bayesian method in TDM of various drugs with narrow therapeutic ranges³⁾. Population pharmacokinetic parameter estimation is a useful tool to evaluate the drug concentrations and to estimate each patient's pharmacokinetic parameters by limited sampling points^{11,12)}. However, in this method, computer utilities are essential in the analytical processing. On the other hand, in a daily practice, computers are not always available. Unfortunately, the use of TDM often follows an "all or none" pattern ; some physicians rarely use it and others use it excessively¹³⁾. The C/D ratios

are easily calculated at bedside or at clinics. Rough evaluation of the patients' response to drug may be possible by monitoring C/D ratios, and changes in drug compliance or pharmacokinetics can be estimated.

In conclusion, by looking at the patients' C/D ratio, we propose that the patient's clinical background is possibly related to the patient's drug compliance, or pharmacokinetics. The C/D ratio may be a useful tool to evaluate the patient's drug compliance and pharmacokinetics in daily bedside therapeutic drug monitoring.

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