Predicting Serum Lithium Concentration Using Bayesian Method: A Comparison with Other Methods

Shun HIGUCHI,* Ryuichi FUKUOKA,** Toshinobu AOYAMA and Masayoshi HORIOKA

Department of Hospital Pharmacy, Faculty of Medicine, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka, 812, Japan

(Received September 5, 1987)

Two pharmacokinetic approaches (single-point Bayesian and two fixed volume of distribution-iterative methods) for predicting serum lithium concentrations in patients treated with lithium carbonate for manic-depressive illness or cyclic neutropenia in Kyushu University Hospital were evaluated and compared retrospectively. Prior to these analyses, three methods (prediction using mean parameters reported by Mason *et al.*, the Pepin method, and the Zetin method) without measuring serum concentrations were also compared. In the Bayesian analysis, the effect of population mean parameters (reported by Mason *et al.* and Pepin *et al.*), which were used as initial estimates in a fitting process, on predictive performance was also studied. Forty five patients (21 male, 24 female) were included in this study. The average number of determinations per patient was 6.3, and the sampling times ranged from 2 to 18 h after the last dose. Serum lithium concentrations were measured by atomic absorption spectrometer. The Bayesian method used a computer program (PEDA) developed previously by one of us.

The prediction using the population mean values from Mason's report gave the least root mean squared error (RMSE; a composite measure for bias and precision of prediction), and was considered to be the most precise among the methods without measuring serum concentrations. Among the methods using a single measured concentration, the Bayesian prediction was less biased and more precise than that by the two fixed volume of distribution-iterative methods. The Bayesian method reduced prediction error in serum concentration prediction compared with those obtained from population mean parameters in both cases: A high reduction of RMSE was observed when the values from Pepin method were used as initial estimates (from 0.320 to 0.219 meq/l), while, Mason's values gave less reduction (from 0.219 to 0.213 meq/l). In the Bayesian prediction of serum lithium concentration, the selection of population-based initial estimates gave no effect on predictive ability of the Bayesian method in terms of RMSE.

In conclusion, the Bayesian method was robust and flexible with regard to dosing schedule, sampling time and number of blood samples, and gave the most clinically acceptable precision among the methods evaluated.

Keywords — blood level; Bayesian method; methodology; lithium; lithium carbonate; prediction; PEDA

Introduction

Lithium carbonate (Li_2CO_3) has been used as a psychotropic agent for the treatment of manic-depressive illness or other psychotropic disorders since the 1970s.¹⁾ It is also well known that patients treated with lithium carbonate for psychosis have neutrophil leucocytosis as one of the side effects. Lithium carbonate has, therefore, been used to prevent or control neutropenia induced in patients suffering from cancer

and treated with chemotherapy.^{2,3)}

Lithium carbonate has a high toxic potential and is considered to have a therapeutic range of 0.6—1.2 meq/l, but some patients may require lower or higher concentrations.¹⁾ For these reasons, slow dosage titration with frequent monitoring of serum concentrations has become a commonly employed method of initiating lithium therapy. However, this approach can be risky as well as time consuming.

Several simplified methods have been pro-

* Author to whom correspondence and requests for reprints should be addressed.

** Present address: *Department of Hospital Pharmacy, Faculty of Medicine, Kagoshima University, 1208-1, Usuki-cho, Kagoshima, 890, Japan.*

posed for prediction and adjustment of the dosage of lithium carbonate. These methods may be divided into two groups, *i.e.*, no need of measuring serum concentrations or not. The former includes the method to calculate the dosage of lithium carbonate from an estimated creatinine clearance⁴⁾ or from a multiple variable linear regression.⁵⁾ The latter includes the single-point method by Cooper *et al.*⁶⁾ and the repeated one-point method by Marr *et al.*⁷⁾

Recently, Sheiner *et al.* have presented a new, sophisticated method, namely the Bayesian method, to predict the pharmacokinetic parameter or the dosage required from a stochastic standpoint.^{8,9)} This Bayesian method has been applied to several commonly used drugs, including theophylline,¹⁰⁾ phenytoin,^{11,12)} lidocaine¹³⁾ and aminoglycosides,¹⁴⁾ but lithium has not been similarly evaluated. The purpose of this study was to assess and to compare the predictive performance of the Bayesian method for predicting serum lithium concentration with those of the other methods.

Patient Selection

The medical charts of approximately 200 psychiatric patients with manic-depressive illness in Kyushu University Hospital were reviewed retrospectively to obtain the data for this study. Patients treated with Li_2CO_3 for cyclic neutropenia were also reviewed. Patient age, sex, status (inpatient or outpatient), concurrent medical diagnosis, or other medications were excluded

from the criteria for patient selection.

Forty-five patients, five of whom had been taking Li_2CO_3 for treatment of cyclic neutropenia, were selected on the basis that they had at least two reliable lithium serum concentrations at different dosing schedules, and the following data were collected: age, sex, weight, height, serum creatinine, dosage and dosing interval, sampling time, and serum lithium concentrations.

Table I summarizes the patient characteristics (the patient's data are given in detail in Appendix A). All serum concentrations were measured in duplicate by atomic absorption spectrometer according to the method described by Pandey (shown in appendix in the reference 7) with a slight modification. The assays were performed in the research division of the hospital pharmacy, and the coefficient of variation was less than 2% in the clinically encountered range of serum concentration.

Pharmacokinetic Consideration

All patients in this study were taking lithium carbonate in divided daily doses, from two to four times a day, at unequally spaced intervals during a 24 h period. For such cases, using a one-compartment open model, serum lithium concentrations can be described by the following equations:¹⁵⁾

TABLE I. Description of Patient Population in Lithium Study ($n = 45$ ^{a)})

Descriptor	Range	Mean $\pm$ S.D.
Determinations/patient ^{b)}	2 – 15	5.9 $\pm$ 2.3
Age (years)	2.3 – 74.1	33.6 $\pm$ 17.6
Weight (kg)	14.1 – 82.5	56.8 $\pm$ 14.2
Serum creatinine (mg/dl)	0.3 – 1.9	0.9 $\pm$ 0.22
Dose (mg/d)	100 – 1500	802 $\pm$ 280
Concentration (meq/l)	0.04 – 1.42	0.54 $\pm$ 0.23

^{a)} 21 patients were male and 23 patients were outpatients at the time of the most recent lithium determination, and some of whom have also experienced hospitalization (details are shown in Appendix A). ^{b)} Total number of determinations were 283.

$$C_p(I, t) = \sum_{i=1}^n \left[\frac{F \cdot D(i) \cdot k_a}{V_d (k_a - k_e)} \left\{ \left(\frac{1 - e^{-I k_e 24}}{1 - e^{-k_e 24}} \right) e^{-k_e t_i} - \left(\frac{1 - e^{-I k_a 24}}{1 - e^{-k_a 24}} \right) e^{-k_a t_i} \right\} \right] \quad (1)$$

$$t_i = t - \sum_{j=0}^{i-1} \tau_j; \sum_{i=1}^n \tau_i = 24; \text{ if } t_i < 0, t_i = t_i + 24$$

where I is the number of periods, n is the number of dosing interval in the period, and the sum of each dosing interval is equal to the length of the period (24 h). F is the fraction of the oral dose absorbed, $D(i)$ is the maintenance dose given at i th dosing, τ_i is the dosing interval between i th dosing and $I+i$ th dosing in the period. V_d is the volume of distribution and k_a is the absorption rate constant. $C_p(I, t)$ is the serum drug concentration at time t , from the beginning of the first dosage, in the I th period. In construction of the model for such cases, the doses administered at the same time of each period during multiple dosing can be estimated as doses given in the 24 h period.

Assuming $k_a \gg k_e$, or at the post absorption and distribution phase, serum drug concentration can also be described by the equation of the reduced form of Eq. 1:

$$C_p(I, t) = \frac{F}{V_d} \left(\frac{1 - e^{-I k_e 24}}{1 - e^{-k_e 24}} \right) \sum_{i=1}^n D(i) \cdot e^{-k_e t_i} \quad (2)$$

The abbreviations are the same as described for Eq. 1. For both Eq. 1 and Eq. 2, the time intervals (*i.e.*, τ_j) entered into the calculations were set at 10 and 14 h for a two times-daily schedule, 5, 5 and 14 h for a three-times-daily schedule, and 5, 5, 3, and 11 h for a four-times-daily schedule, regardless of the patient's actual dosing schedules.

In clinical settings, the dosing schedule rarely follows an ideal schedule, however, assuming equally given dosages and spaced dosing intervals, a simpler and more conventional formula was given as following equation:

$$C_p(I, t) = \frac{F \cdot D}{V_d} \left(\frac{1 - e^{-I k_e \tau}}{1 - e^{-k_e \tau}} \right) e^{-k_e t} \quad (3)$$

D is the maintenance dose assumed to be given equally at each dosing interval, and τ is dosing interval assumed to be equally spaced. Other abbreviations are the same as those described above. Eq. 1 was used for the Bayesian method, and Eq. 2 and Eq. 3 were used for the fixed volume of distribution-iterative method.

Predictive Methods

PART I — The predictive ability of the three methods, Mason, Pepin and Zetin methods, based on population estimates without concentration measurements were compared prior to the Bayesian analysis.

Mason Method — Using the mean values from the report of Mason *et al.*,¹⁷⁾ the population estimates of CL_{Li} and V_d were obtained by the following formulas: $CL_{Li} = 0.021$ ABW; $V_d = 0.79$ ABW, where ABW is the actual body weight in kg, CL_{Li} is the lithium clearance in l/h, and V_d is the volume of distribution in l. After derivation of k_e from the formula; $k_e = CL_{Li}/V_d$, the serum lithium concentration was predicted from Eq. 1.

Pepin Method — Pepin *et al.* assumed that CL_{Li} was 23.5% of the creatinine clearance (CL_{cr}) derived from the Cockcroft-Gault equation.¹⁸⁾ Pepin *et al.* have used the ideal body weight (IBW) in estimation of CL_{cr} . In this study, however, ABW was substituted for IBW because neither severe obese nor lean subjects were included in our study patients. For children of less than 15 years in age, CL_{cr} was estimated from the formula of Schwartz *et al.*¹⁹⁾ The details of the method are described in Appendix B.

The serum lithium concentrations were calculated from Eq. 1 after obtaining the values of the parameters. In both the Mason and the Pepin method, k_a was arbitrarily set at 1.5 h^{-1} in calculating serum concentrations from Eq. 1.

Zetin Method — Zetin *et al.* have proposed a simple mathematical model for dosage calculation of Li_2CO_3 to achieve concentration of 1 meq/l using a technique of stepwise multiple regression analysis.⁵⁾ The prediction method is based on the patient's sex, age, weight, lithium dosage form, and concomitant tricyclic antide-

pressant therapy. In our study, serum lithium concentrations were estimated from the rearrangement of the Zetin model (see Appendix B).

Only samples ($n = 219$) drawn at steady state, at least 7 d later after initiation, were entered in this analysis.

Part II — The Bayesian method using two population mean values (Mason and Pepin methods in Part I) as initial parameter estimates and the fixed volume of distribution-iterative methods with two variations with respect to pharmacokinetic equations, Eq. 2 and Eq. 3 (designated as Iterative I and Iterative II, respectively), were evaluated and compared. All methods were performed using one concentration measurement.

Bayesian Method — The theoretical basis of the Bayesian method has been described in detail elsewhere.^{8,9,20} The objective function of the Bayesian method in this study is the following:

$$O_{bj} = \sum_{i=1}^n \frac{(C_i - \hat{C}_i)^2}{\sigma_{C_i}^2} + \frac{(CL - \hat{CL})^2}{\sigma_{CL}^2} + \frac{(V_d - \hat{V}_d)^2}{\sigma_{V_d}^2} + \frac{(k_a - \hat{k}_a)^2}{\sigma_{k_a}^2}$$

where $\hat{CL}$, $\hat{V}_d$ and $\hat{k}_a$ are the population mean values, CL , V_d and k_a are the individual parameter estimates, C_i is drug concentration measurement, $\hat{C}_i$ is the predicted drug concentration for the i th observation and n is the total number of concentration measurements. σ_{CL}^2 , $\sigma_{V_d}^2$ and $\sigma_{k_a}^2$ are the prior, inter-individual variance for the CL , V_d and k_a , respectively, and $\sigma_{C_i}^2$ is referred to as the conditional, residual error variance of the C_i attributable to both assay error and intra-individual variability.

The Bayesian analysis was carried out on a microcomputer program PEDDA, which was developed previously by one of us,^{12,15} using one concentration measurement.

As has been reported,^{9,20} the values of the coefficient of variation (CV) for CL and V_d in the general population were considered to be in the range of 40–50% and 10–20%, respective-

ly. Thus, in this study, the values of σ_{CL} and σ_{V_d} were set at 50 and 20% of CL and V_d (the upper level of each range), respectively, because there are no available variance at hand. σ_{k_a} was set at 70%.²⁰ Measured concentrations were weighted by 15% of CV. The predictions by revised parameter estimates, thereafter, were repeated in a patient for other observations except for the one point used to estimate the individual parameters. This was repeated for all subjects and observations.

Iterative Method — The iterative method proposed by Mungall *et al.*²¹ and Koup *et al.*²² estimates the parameter of concern using an iterative computer program, which repeatedly calculates serum concentration in the equation by changing the parameter term with an appropriate step size until the difference between the calculated and the measured concentration reach a minimum value. In this study, the volume of distribution was fixed at 0.79 l/kg through the iteration process in both Iterative I and Iterative II, and the elimination rate constant was modified by Newton's method²³ on a microcomputer. The subsequent steps were the same as described in the Bayesian Method.

Data Analysis

The relationship between measured and predicted concentrations was evaluated using least squares linear regression. The predictive ability of the methods was evaluated, as was presented by Sheiner and Beal,²⁴ by calculating mean prediction error (ME) as a measure of bias, mean absolute prediction error (MAE) as a measure of accuracy, and root mean squared error (RMSE) as a composite measure of bias and precision. ME, MAE and RMSE were calculated as follows:

$$ME = \frac{1}{n} \sum_{i=1}^n Pe$$

$$MAE = \frac{1}{n} \sum_{i=1}^n |Pe|$$

$$RMSE = \left\{ \frac{1}{n} \sum_{i=1}^n Pe^2 \right\}^{1/2}$$

where Pe is the prediction error (predicted concentration minus measured concentration) and n is the number of pairs of concentrations. A probability level less than 0.05 was considered significant. Comparison of the relative predictive performance was evaluated by comparing 95% confidence intervals.

Results and Discussions

The correlation coefficients, mean prediction error (ME), root mean squared error (RMSE), and their respective 95% confidence limits for predicted serum lithium concentrations based on the population estimates are shown in Table II.

The correlation coefficients ranged from 0.454 to 0.607 and were significantly ($p < 0.05$) different from zero. The prediction using the Mason parameters (RMSE = 0.219 meq/l) was significantly more precise ($p < 0.05$) when compared with those from either the Pepin method (RMSE = 0.320 meq/l) or the Zetin method (RMSE = 0.322 meq/l) by approximately 45%. Both the Mason and Pepin methods significantly overpredicted the measured concentration (*i.e.*, the 95% confidence interval of the mean prediction error did not include zero), and the prediction by the Pepin method (ME = 0.147 meq/l) was significantly ($p < 0.05$) more biased than that by the Mason parameters (ME = 0.069 meq/l). The Zetin method, however, significantly underpredicted the measured concentration ($p < 0.05$). The prediction by using the Mason parameters, thus, was considered to

be the most precise among the methods without measuring concentration. These results, except those from the Mason method, are similar to those of Patrias and Moore²⁵ (Mason's mean values has not been evaluated in the population study). Patrias and Moore reported, using the same size population as ours, that the Pepin method underpredicted the actual dosage (*i.e.*, overprediction of measured concentration), while the Zetin method overpredicted the dosage (*i.e.*, underprediction of measured concentration).

Figure 1 illustrates the relationships between the prediction error obtained from the three methods *a priori* and age, and Fig. 2 the prediction error and serum creatinine.

The Mason method shows a negative correlation between the prediction error and age ($r = -0.441$, $p < 0.01$) and between the prediction error and serum creatinine ($r = -0.375$, $p < 0.01$), and overpredicted the actual concentration in a population of less than 15 years old or of low serum creatinine level. This indicates that without concentration measurements the Mason parameters are not appropriate for predicting the serum lithium concentration of children whose serum creatinine level is usually low compared with that of adults. It also suggests that the lithium clearances in children are likely to be more rapid than adults. The further study on the pharmacokinetics of lithium in children should be required.

The Pepin method, on the other hand, shows positive correlations ($r = 0.396$ for age, $p < 0.01$; $r = 0.324$ for serum creatinine, $p < 0.01$)

TABLE II. Summary of Predictive Performance for Various Methods without Measuring Serum Lithium Concentrations

Method	Predictions ^{a)}	r ^{c)}	ME (meq/l) ^{d,g)}	RMSE (meq/l) ^{d,h)}
Pepin	0.69 ± 0.33 (280)	0.541	0.147 (0.114, 0.181) ^{e)}	0.320 (0.284, 0.352)
Mason	0.61 ± 0.24 (280)	0.607	0.069 (0.045, 0.094) ^{e)}	0.219 (0.194, 0.242)
Zetin	0.54 ± 0.35 (219) ^{b)}	0.454	-0.056 (-0.098, -0.014) ^{f)}	0.322 (0.290, 0.351)

a) Each value is expressed as the mean ± S.D. Values in parentheses are the numbers of predictions. *b)* The mean of the actual lithium concentration is 0.59 ± 0.22 meq/l. *c)* r refers to the correlation coefficient between predicted and measured concentrations. *d)* Values in parentheses are the lower and upper 95% confidence intervals. *e)* Significantly overpredicted the measured concentrations. *f)* Significantly underpredicted the measured concentration. *g)* Significant differences were observed for the following comparisons of bias: Pepin *versus* Mason, Pepin *versus* Zetin, and Mason *versus* Zetin. *h)* Significant differences were observed for the following comparisons of precision: Mason *versus* Pepin, and Mason *versus* Zetin.

Fig. 1. Scatter Diagrams of Prediction Error *versus* Age Used in Making the Prediction of Serum Lithium Concentration for the Mason Method, the Pepin Method and the Zetin Method

Broken lines indicate regression lines: Mason, error = $0.233 - 0.005 \times \text{age}$; Pepin, error = $-0.053 + 0.006 \times \text{age}$; Zetin, error = $-0.251 + 0.002 \times \text{age}$

though it gave larger prediction errors than the Mason method. Pepin method⁴⁾ utilizes an estimated creatinine clearance derived from sex, age, ideal body weight and serum creatinine value using the Cockcroft-Gault equation. In our present study, actual body weight was used instead of ideal body weight and the Schwartz

Fig. 2. Scatter Diagrams of Prediction Error *versus* Serum Creatinine Used in Making the Prediction of Serum Lithium Concentration for the Mason Method, the Pepin Method and the Zetin Method

Broken lines indicate regression lines: Mason, error = $0.386 - 0.351 \times \text{Scr}$; Pepin, error = $-0.216 + 0.402 \times \text{Scr}$; Zetin, error = $-0.082 - 0.099 \times \text{Scr}$

equation was used for estimating the creatinine clearance of children of less than 15 years. Patrias and Moore demonstrated that substitution of actual body weight for ideal body weight had no effect on improvement of predictive ability.²⁵⁾ The results indicate that the Pepin method was not appropriate for our study popu-

lation. As suggested by the scattergram obtained using the Pepin method in Fig. 2, the relatively poor predictability of this method in our study may be due to the means used for estimation of creatinine clearance rather than the principle of the Pepin method itself.

The Zetin method shows neither age nor serum creatinine related predictability ($r = 0.124$ for age, $p > 0.05$; $r = -0.06$ for serum creatinine, $p > 0.05$) and the method tended to underpredict the serum concentrations over the patients. The direction of prediction error is also important to consider. Underprediction of serum concentration (*i.e.*, overprediction of actual dosage) carries the risk of producing toxicity, while overprediction may provide less than optimal therapy. Therefore, it is likely that the predicted dosage using the Zetin equation can cause an overdosage in the Japanese population.

The sex and the patient status (*i.e.*, inpatient or outpatient) had no effects on predictability in our study.

Table III shows predictive performance of the methods using one concentration measurement. Both iterative methods evaluated in this study gave not only very poor correlations between measured and predicted concentration but also large values of prediction error (0.503 meq/l of RMSE by Iterative I; 0.873 meq/l of RMSE by Iterative II) with positive bias.

The results from the iterative methods are not unexpected. The equations for iterative methods were simpler than that for the Bayesian

method. Thus, these results showed a flexibility or suitability of the Bayesian method to incorporate complex mathematical expressions such as Eq. 1 in clinical practice.

In the dosage prediction study of theophylline, Mungall *et al.*²¹⁾ and Koup *et al.*²²⁾ reported that the fixed volume of distribution-iterative method gave good precision in subsequent dosage calculation using serum concentrations obtained from intravenous administration of theophylline. The poor predictive ability in the iterative methods might be due to unrestricted conditions in our study, such as dosing schedule or sampling time (ranged from 2 to 18 h after the last dose in our study population). These results also demonstrated that these conventional methods to predict serum drug concentration or dosage requirement can result in an unacceptable precision in clinical practice with no regard for dosing schedule or sampling time.

The Bayesian method was considered to be less biased and more precise than not only the two fixed volume of distribution-iterative methods but also population-based predictive methods. Regardless of the population-based mean parameters used as initial estimates, the Bayesian method reduced the prediction error for serum concentration in both cases compared with the predictive method based on population estimates. The high reduction of RMSE was observed in the use of the Pepin method (from 0.320 to 0.219 meq/l) which had given poor precision without feedback of measurements. On the other hand, the prediction using Mason's

TABLE III. Predictive Performance of the Bayesian and the Fixed Volume of Distribution-Iterative Methods in Predicting Serum Lithium Concentrations

Method	$r^a)$	ME (meq/l) ^{b,d)}	RMSE (meq/l) ^{b,e)}
Bayesian (Pepin)	0.575	0.025 (0.015, 0.035)	0.219 (0.205, 0.232)
Bayesian (Mason)	0.583	0.015 (0.005, 0.024)	0.213 (0.200, 0.226)
Iterative I	0.261	0.031 (0.008, 0.054)	0.503 (0.312, 0.705)
Iterative II	0.151	0.132 (0.092, 0.173)	0.873 (0.698, 1.018)

a) r refers to the correlation coefficient between predicted and measured concentrations. b) Values in parentheses are the lower and upper 95% confidence intervals. c) Significantly overpredicted the measured concentrations. d) Significant differences were observed for the following comparisons of bias: Pepin *versus* Iterative II, Mason *versus* Iterative II, and Iterative I *versus* II. e) Significant differences were observed for the following comparisons of precision: Bayesians *versus* Iterative I, and Bayesians *versus* Iterative II.

Fig. 3. Reduction of Percent Absolute Prediction Error

Clear bars refer to prediction error by population-based mean parameters. Hatched bars refer to single-point Bayesian method. Vertical lines indicate $\pm$ SEM. Reduction of %MAE was: Mason, from 30.3 to 26.2%; Pepin, from 44.4 to 26.6%.

values gave less reduction (from 0.219 to 0.213 meq/l) which had provided good precision without measured concentrations. There was no significant difference between these two methods in terms of RMSE. Figure 3 shows the reduction of mean absolute prediction error (MAE) in both cases.

It can be understood readily from the theoretical basis of the Bayesian method that the predictive performance of the Bayesian method is sensitive to population or subpopulation parameter values, mean and variance, and some literatures pointed out this in actual cases.^{9,28)} In our lithium study with the two kinds of population mean values but the same variance, however, no significant difference in predictive performance was found between the two population mean values in terms of both bias and precision, and the results were slightly inconsistent with previously reported results for other drugs such as phenytoin,¹⁶⁾ carbamazepine,²⁶⁾ and valproic acid²⁷⁾ in which the effects of parameter choice on predictive performance were indicated. Al-

though no clear reason for this discrepancy was obtained at present, the characteristics of population studied should be considered. As shown in Fig. 1, our study population ranged widely in age, from 2 to 74, while the previous study included a relatively narrow aged population (e.g., children or adults). A further study, especially on a stratified subpopulation such as age, is required. Furthermore, as suggested by D'Argenio *et al.* in their simulation work of theophylline,²⁸⁾ the selection of variance value as well as population mean value must be evaluated when accurate variance values become available.

The Bayesian method overpredicted the measured concentration significantly in both cases (0.025 meq/l of ME by the Pepin; 0.015 meq/l by the Mason, $p < 0.05$). This tendency is favorable for clinical settings because of less risk of overdosage. The upper value of 95% confidence interval of RMSE by the Bayesian method is approximately 0.23 meq/l. This means that if the desired concentration is targeted to 0.85 meq/l of serum lithium concentration, 95% of the serum lithium concentrations will fall within the therapeutic range of 0.62 to 1.08 meq/l by the single-point Bayesian method.

So far, the predictive performance of the Bayesian method has been evaluated mostly with the hospitalized patient population, while our study population included a large number of outpatients, whose actual dosing history could be rarely ascertained and thus were frequently unreliable. Furthermore, in several patients, our analyses included the predictions which have a long period of time between the point of observation used for obtaining the patient's parameters and the point of prediction (see Appendix A). So, our population study included a relatively large intra-individual variability attributable to unreliability of dosing history and temporal change of patient's disease state or pharmacokinetic condition in addition to inter-individual variability as a source of prediction errors. Nevertheless, only the Bayesian method based on the stochastic principle gave clinically acceptable predictions. Our results, therefore, revealed the great capacity of the Bayesian method to deal with such uncertainties which

existed in routine clinical practice.

On the whole, it was concluded that the Bayesian method was robust and flexible with regard to dosing schedule, sampling time and number of samples, in predicting serum lithium concentrations and would provide clinically acceptable

precision even in outpatient settings.

Acknowledgements We would like to thank Hiromi Mihara for her secretarial assistance, and Hideki Shuto for his technical assistance.

Appendix A. Details and Dosing Schedule of Li_2CO_3 Taken Patients

Pt. No.	No.	Sta-tus ^{a)}	Sex ^{b)}	Age ^{c)} (years)	Wei-ght (kg)	Hei-ght (cm)	S_{cr} ^{d)} (mg/dl)	Dose (mg) ^{e)}				Serum conc. (meq/l)	Time and dosing interval at observation ^{f)}
								1st	2nd	3rd	4th		
1	1	in	f	16.5	51	163	1.0	400	200	400	200	0.62	13h - 4th
	2	in		17.0	55	163	1.9	400	200	400	200	0.91	13h - 4th
	3	in		17.0	55	163	1.7	400	200	400	200	0.72	13h - 4th
	4	in		17.0	55	163	1.0	300	300	300	300	0.56	13h - 4th
	5	in		17.1	56	163	1.0	300	300	300	300	0.76	4h - 2nd
	6	in		17.5	48	163	1.0	300	300	300	300	1.18	2.5h - 2nd
	7	in		17.5	51	163	0.8	300	300	300	300	0.71	4h - 1st
	8	in		18.4	47	165	0.8	300	300	300		0.62	5h - 1st
	9	in		18.6	49	165	0.8	300	300	300		0.60	14h - 3rd
	10	in		18.9	56	167	0.5	300	300	300		0.63	14h - 3rd
	11	in		19.0	56	167	0.5	300	300	300		0.49	14h - 3rd
	12	in		19.1	56	167	0.8	300	300	300		0.55	14h - 3rd
	13	in		19.2	45	167	0.9	300	300	300		0.72	14h - 3rd
	14	in		19.7	47	164	0.8	300	300	300		0.52	14h - 3rd
	15	in		19.9	47	164	0.8	300	300	300		0.74	14h - 3rd
2	1	out	m	51.8	72	163	0.9	200		200		0.29	14h - 2nd
	2	out		52.1	66	164	0.9	200		200		0.22	14h - 2nd
	3	out		52.2	67	164	0.9	200	200	200		0.45	14h - 3rd
3	1	out	f	21.1	51	160	0.8	200	200	200		0.47	11h - 3rd
	2	out		21.1	52	153	0.8	400	200	200		0.64	11h - 3rd
	3	out		21.3	57	158	0.9	400		400		0.35	14h - 2nd
	4	out		21.6	55	158	0.9	400		400		0.40	14h - 2nd
	5	out		22.9	62	158	0.8	400		400		0.65	14h - 2nd
	6	out		23.1	63	158	1.1	400		400		0.61	14h - 2nd
4	1	out	f	18.2	52	157	0.7	400	400	200		0.76	13h - 3rd
	2	out		18.2	51	157	0.6	400	200	200		0.54	13h - 3rd
	3	out		18.3	55	157	0.7	200	200	200		0.54	13h - 3rd
	4	out		18.3	56	157	0.8	200		200		0.39	13h - 2nd
	5	out		18.3	54.5	157	0.7	400	200	200		0.66	13h - 3rd(2d)
5	1	out	f	20.2	54	154	0.9	400	400	400		0.86	12h - 3rd
	2	out		20.2	54	154	0.9	600	400	400		1.13	12h - 3rd

	3	out		20.2	54	154	0.9	600	400	400		0.86	12h - 3rd
	4	out		20.2	53	154	0.8	400	400	400		0.59	14h - 3rd(6d)
	5	out		20.4	55	154	0.7	400	400	400		0.76	11h - 3rd(4d)
	6	out		20.5	59	154	0.7	400	400	400		0.73	14h - 3rd
6	1	out	f	37.9	64	159	0.7	200	200	200		0.35	11h - 3rd
	2	out		38.0	62	160	0.7	200	200	200	200	0.42	10h - 4th
	3	out		38.0	64	159	0.7	200	200	200		0.70	11h - 3rd
	4	out		38.0	64	158	0.8	200	200	200		0.79	11h - 3rd
7	1	out	m	37.7	62	163	1.1	400	200	200		0.47	11h - 3rd(4d)
	2	out		37.7	62	163	1.1	400	200	200		0.57	11h - 3rd
	3	out		37.7	62	163	1.1	400	300	300		0.80	11h - 3rd(5d)
	4	out		37.8	62	163	1.1	400	300	300		0.92	11h - 3rd(6d)
	5	out		37.8	56	163	1.1	200	400	200		0.53	12h - 3rd
	6	out		37.9	60	163	0.9	200	400	200		0.57	12h - 3rd
	7	out		38.0	53	163	0.9	200	400	200		0.55	12h - 3rd
8	1	out	f	73.6	41	148.5	0.8	200	200	200		0.63	10h - 3rd
	2	out		73.6	41	148.5	0.8	400	400	200		1.20	10h - 3rd
	3	out		73.7	41	148.5	0.8	100		100		0.23	10h - 2nd(5d)
	4	out		73.7	41	148.5	0.8	100		100		0.23	10h - 2nd
	5	out		73.7	41	148.5	0.8	100	100	100		0.66	10h - 3rd(4d)
	6	out		73.7	41	148.5	0.9	100	100	100		0.46	10h - 3rd
	7	out		73.8	41	148.5	0.9	100	100	100	100	0.54	10h - 4th
	8	out		73.9	41	148.5	0.7	100	100	100	100	0.56	4h - 1st
	9	in		74.1	41	148.5	0.8	100	100	100	100	0.31	3h - 1st(3d)
9	1	in	f	29.1	60	155	0.7	200	200	200		0.30	14h - 3rd
	2	in		29.3	60	155	0.7	200	200	200		0.25	14h - 3rd
	3	in		29.4	59	155	0.7	300		300		0.27	14h - 2nd
	4	in		29.7	58	155	0.7	400	200	400		0.51	14h - 3rd
	5	in		30.0	58	155	0.7	400	200	200		0.34	14h - 3rd
	6	in		30.4	60	155	0.8	400	400	400		0.64	14h - 3rd
	7	in		30.4	60	155	0.8	400	400	400		0.63	14h - 3rd
	8	in		30.5	60	155	0.9	400	400	400		0.68	14h - 3rd
	9	in		30.9	58	155	0.9	400	400	400		0.66	14h - 3rd
	10	in		31.0	59	155	0.9	400	400	400		0.67	14h - 3rd
	11	in		31.7	61	155	0.9	400	400	400		0.60	14h - 3rd
10	1	in	m	20.4	75	174	0.8	200		200		0.09	11.5h - 2nd
	2	out		20.5	76	174	1.0	200	200	400		0.18	14h - 3rd
	3	out		20.5	77	174	1.0	400	200	400		0.29	14h - 3rd
	4	out		20.5	77	173	1.0	400	400	400		0.32	14h - 3rd(5d)
	5	out		20.6	77	173	1.0	400	200	400	400	0.49	11.5h - 4th(6d)
	6	out		20.9	80	173	1.0	600				0.11	14h - 1st
11	1	out	m	20.2	47	156	1.0	200	200	200	200	0.32	11h - 4th(1d)
	2	out		20.3	52	156	1.0	200		400		0.27	14h - 2nd
	3	out		20.3	47	156	1.0	200	200	200	200	0.86	11h - 4th(5d)
	4	out		20.3	49	156	1.3	400	400	400		0.55	14h - 3rd
	5	out		20.3	52	156	1.0	400	400	400		0.65	14h - 3rd
	6	out		20.4	52	156	1.0	400	400	400		0.67	14h - 3rd

	7	out		20.4	54	156	1.1	400	400	400		0.80	14h - 3rd
	8	out		20.5	53	156	1.0	200	400	400		0.67	14h - 3rd(6d)
	9	out		20.7	54	157	1.0	200	200	200		0.21	14h - 3rd
	10	out		20.9	54	156	1.0	200		400		0.33	12h - 2nd
12	1	out	f	26.2	65	154	0.9	400	200	200		0.46	14h - 3rd(2d)
	2	out		26.3	63	154	0.9	400	200	400		0.56	14h - 3rd
13	1	in	m	51.8	77	168	1.1	300	300	300		0.70	14h - 3rd(5d)
	2	out		51.8	77	168	1.1	400	400	400		0.58	14h - 3rd(5d)
	3	out		52	80	170	1.1	400	400	400		0.70	3h - 1st
	4	out		52.1	79	170	1.1	400	400	400		0.44	14h - 3rd
	5	out		52.1	80	170	1.0	400	400	400		0.63	2.5h - 1st
	6	in		52.3	81	170	1.0	400	400	400		0.40	14h - 3rd
	7	in		52.7	78	170	0.9	400	400	400		0.91	2.5h - 1st
	8	in		52.8	77	170	1.2	400	400	400		0.57	14h - 3rd
	9	in		53.9	80	170	1.1	400	200	400		0.46	14h - 3rd
	10	in		53.0	80	170	1.1	400		400		0.46	14h - 2nd
14	1	in	m	52.6	60	160	1.0	400	400	400		0.93	2.5h - 1st
	2	in		52.8	67	165	1.0	200	200	400		0.53	12.5h - 3rd
	3	in		53.0	62	165	0.9	200	200	200		0.45	14h - 3rd
	4	in		39.8	52	158	0.8	200	200	200		0.33	3h - 1st
	5	in		39.8	52	158	0.8	200		200		0.18	14h - 2nd
	6	in		58.3	75	165	1.1	200	200	200		0.62	3h - 1st
	7	in		59.0	74	164	1.0	400	200	200		0.32	14h - 3rd
	8	in		59.1	72	164	1.0	200	200	200	200	0.49	10.5h - 4th
15	1	in	f	50.5	61	156	0.8	200	200	200		0.26	14h - 3rd
	2	in		50.6	59	157	0.8	200	200	200	200	0.24	14h - 4th
	3	out		51.1	70	156	0.7	200	200	200	200	0.50	11h - 2nd
	4	in		53.9	61	156	0.8	200	200	200		0.30	14h - 3rd
16	1	out	m	22.5	54	163	1.0	200	200	400		0.60	14h - 3rd
	2	out		22.5	56	163	0.9	200	200	400		0.76	14h - 3rd
	3	out		22.5	54	163	1.2	200	200	200		0.49	14h - 3rd(5d)
	4	out		22.5	54	163	1.1	200	200	200		0.47	14h - 3rd
17	1	in	f	23.9	68	162	0.8	200	200	400		0.66	14h - 3rd
	2	out		23.9	69	162	0.8	200	200	400		0.58	14h - 3rd
	3	out		24.0	63	170	0.9	200	200	400		0.89	14h - 3rd
	4	out		24.0	75	170	1.3	200	200	400		0.85	14h - 3rd
	5	out		24.1	56	162	0.9	200	200	200	200	0.79	11h - 4th
	6	out		24.2	56	162	0.9	200	200	200	200	0.60	11h - 4th
	7	out		24.6	62	162	0.8	200	200	200	200	0.48	12h - 4th
	8	in		24.7	61	162	0.8	200	200	200		0.30	9h - 3rd
	9	in		24.8	60	163	0.8	200	200	200	200	0.45	4.5h - 1st
18	1	in	m	42.6	66	172	1.0	300	200	200		0.61	3.5h - 1st
	2	out		43.7	68	170	1.3	200	200	200		0.64	14h - 3rd
	3	out		43.7	67	170	1.1	400	200	200		0.84	14h - 3rd
	4	out		43.8	67	170	1.0	400	200	400		1.01	14h - 3rd(3d)
	5	out		43.8	67	170	1.1	400	200	400		1.04	14h - 3rd

	6	out		43.9	70	170	1.1	200	200	400		0.78	14h - 3rd
	7	out		44.0	67	170	1.1	200	200	400		0.79	14h - 3rd(5d)
	8	in		45.4	69	172	1.0	400		200		0.55	3.5h - 1st
19	1	in	m	28.9	61	167	0.9	200	200	200		0.40	13h - 3rd
	2	in		29.0	62	167	0.9	200	200	400		0.50	11h - 3rd
	3	in		29.9	64	166	0.9	200	200	200		0.29	14h - 3rd
	4	out		31.3	64	166	0.9	200	200	200	200	0.61	11.5h - 4th
	5	out		31.3	64	166	1.0	400	200	200	400	0.84	11.5h - 4th
	6	out		31.4	64	166	1.0	400	200	400	400	0.98	11.5h - 4th
	7	out		31.4	64	166	1.0	200	200	400	400	0.85	11h - 4th(5d)
	8	out		31.4	64	166	1.0	200	200	200		0.36	11h - 3rd
	9	out		31.5	62	166	1.0	200		200		0.22	12h - 2nd
20	1	out	m	54.5	56	161	1.2	200	200	200		0.44	12h - 3rd(5d)
	2	out		54.5	58	164	1.1	200	200	200		0.44	14h - 3rd(3d)
	3	in		54.6	56	161	1.1	400		400		0.37	16h - 2nd
21	1	out	f	27.7	52	153	1.0	200	200	200		0.21	16h - 3rd
	2	out		27.8	52	153	1.0	400		400		0.04	16h - 2nd
	3	in		28.1	53	154	1.0	200				0.16	3.5h - 1st
	4	in		28.7	51	154	1.0	200		200		0.33	5h - 1st(3d)
22	1	in	f	68.5	46	146	0.6	400		400		0.42	14.5h - 2nd
	2	out		69.8	42	146	0.8	300	300	300		0.84	11h - 3rd(2d)
	3	out		69.9	42	146	0.7	300	300	300		0.87	15h - 3rd
	4	out		71.6	44	146	0.7	200		200		0.37	14h - 2nd(4d)
23	1	in	m	16.7	45	168	0.6	400		200		0.56	3h - 1st
	2	in		16.8	45	168	0.6	400	200	400		0.77	4h - 1st
	3	in		17.0	51	166	0.6	400	200	400		0.68	4h - 1st
	4	in		17.4	53	170	0.8	400	200	400		0.59	4h - 1st
	5	in		17.9	59	170	0.8	400	200	400		0.42	14h - 3rd
	6	in		18.2	55	171	1.0	400	200	400		0.63	3h - 1st
24	1	in	m	47.1	68	168	1.0	400		400		0.46	9h - 1st
	2	out		47.6	66	168	1.4	100	100	100		0.12	14h - 3rd(1d)
	3	out		47.6	64	168	1.4	200	200	200		0.42	14h - 3rd(5d)
	4	out		47.6	65	168	1.2	300	300	300		0.48	14h - 3rd
	5	out		47.6	64	168	1.2	400	400	400		0.64	14h - 3rd(1d)
	6	out		48.8	62	168	1.2	200	200	200	200	0.36	11h - 4th(2d)
	7	out		48.8	63	168	1.2	200	200	200	200	0.48	10h - 4th
	8	out		48.9	63	165	1.0	200	200	200	200	0.54	11h - 4th
25	1	out	f	12.7	45	144	1.1	200	200	200		0.36	14h - 3rd
	2	out		12.7	45	144	0.9	200	200	400		0.52	11h - 3rd(4d)
	3	out		12.8	45	144	0.9	200	200	400		0.55	14h - 3rd
	4	out		12.8	45	144	0.7	200	200	400		0.55	14h - 3rd
	5	out		12.8	45	144	0.7	400	200	400		0.68	14h - 3rd(2d)
	6	out		12.8	49	144	0.8	400	200	400		0.79	14h - 3rd
	7	out		12.9	50	144	0.8	400	200	400		0.61	14h - 3rd
	8	out		12.9	50	144	0.7	400	200	400		0.61	14h - 3rd
	9	out		12.9	50	144	0.8	400	200	400		0.49	14h - 3rd

	10	in		13.0	50	144	0.7	400	400	0.70	7h - 1st		
	11	in		13.1	52	145	1.2	400	400	0.51	17h - 2nd		
	12	in		13.3	50	145	0.8	400	400	0.90	2h - 1st		
	13	in		13.4	55	147	0.7	400	400	0.84	3h - 1st		
	14	in		13.9	57	148	1.0	400	200	0.54	4h - 1st		
	15	in		14.0	58	148	0.9	400	200	0.41	15h - 2nd		
26	1	out	f	29.9	65	155	0.7	200	200	200	0.44	14h - 3rd	
	2	in		29.9	55	161	1.1	200	200	200	0.17	14h - 3rd(4d)	
	3	out		30.2	58	162	0.6	200	200	200	0.48	14h - 3rd	
	4	out		30.2	59	161	0.6	200	200	200	0.47	14h - 3rd	
	5	out		30.9	64	161	0.8	400		400	0.56	14h - 2nd	
	6	out		31.0	63	161	0.8	400		400	0.56	11h - 2nd	
27	1	in	m	47.9	72	170	1.2	200	200	400	0.42	6.5h - 1st	
	2	in		48.9	72	170	1.2	400		400	0.12	15h - 2nd	
28	1	in	m	53.9	58	162	1.2	200	200	200	0.32	14h - 3rd(3d)	
	2	in		53.9	58	162	1.2	300	300	300	0.52	14h - 3rd(4d)	
	3	in		54.0	58	162	1.2	400	400	400	0.69	14h - 3rd(5d)	
	4	in		54.0	56	162	1.2	400	400	400	0.80	14h - 3rd(6d)	
	5	in		55.1	60	163	1.1	200	200	200	0.31	14.5h - 3rd	
	6	in		55.3	60	162	1.2	400	400	400	0.71	14h - 3rd	
	7	in		55.9	55	163	1.2	400		400	0.40	14.5h - 2nd	
29	1	in	m	46.2	61	165	1.2	400	200	400	0.71	15h - 3rd	
	2	in		46.8	62	165	1.2	300		300	0.76	17h - 2nd	
	3	in		48.3	65	165	1.2	400	400	400	0.84	16h - 3rd	
	4	in		48.9	67	164	1.4	400	200	400	1.21	3h - 1st	
	5	in		48.9	66	164	1.4	400		400	0.51	14h - 2nd	
	6	in		49.2	64	165	1.4	400		400	0.95	3h - 1st	
	7	in		49.6	65	164	1.5	200		200	0.61	16h - 2nd	
30	1	out	m	36.0	74	167	0.9	200	200	200	0.35	14h - 3rd(6d)	
	2	out		36.1	70	167	0.9	200	200	200	0.37	14h - 3rd	
	3	out		36.4	68	167	1.0	100	100	100	0.31	13.5h - 3rd	
31	1	out	m	61.3	82	162	1.0	400	200	200	0.37	10.5h - 3rd	
	2	out		62.7	80	162	1.1	200	200	200	200	0.44	9h - 1st(1d)
32	1	in	f	38.3	57	155	0.9	200	200	200	200	0.27	15.5h - 4th
	2	out		38.5	58	156	0.9	400	200	200	0.36	14h - 3rd	
	3	out		38.9	65	156	0.8	400	200	200	0.94	2h - 2nd	
	4	in		39.3	58	155	0.8	400	200	400	0.60	3h - 1st	
	5	in		39.5	57	155	0.7	400	200	400	0.64	6h - 1st	
	6	in		40.2	60	155	0.7	400	400	400	0.89	3h - 1st	
	7	in		41.3	57	155	0.7	400		400	0.62	3h - 1st	
33	1	out	f	49.6	58	153	0.9	200	200	200	0.26	14h - 3rd	
	2	out		51.2	63	152	1.0	200	200	200	0.24	14.5h - 3rd(1d)	
	3	out		51.2	63	152	1.0	400	200	200	0.36	14.5h - 3rd	
	4	out		51.2	63	152	0.9	400	200	400	0.69	14.5h - 3rd	
	5	out		51.2	63	152	0.9	400	200	400	0.68	14.5h - 3rd	

	6	out		51.4	62	152	1.0	400	200	400		0.68	11h - 3rd
34	1	out	f	30.5	53	156	0.5	200	200	200		0.29	14.5h - 3rd(4d)
	2	in		30.5	54	157	0.5	200	200	200		0.39	2.5h - 1st
	3	in		31.3	52	157	0.7	400		400		0.35	14.5h - 2nd
	4	in		31.8	47	157	0.6	400		400		0.42	15h - 2nd
35	1	out	m	50.3	72	163	1.0	200	200	200		0.32	14.5h - 3rd
	2	out		50.4	72	163	1.0	400	400	400		0.53	14.5h - 3rd(6d)
	3	out		50.4	74	163	1.0	400	400	400		1.03	3h - 1st
	4	out		50.5	74	163	1.0	400	400	400	200	0.89	11.5h - 4th
	5	out		50.6	73	163	1.0	400	400	400	200	0.81	10.5h - 4th
	6	in		50.6	60	160	1.0	400	400	400		0.68	3.5h - 1st
36	1	out	f	70.8	46	137	0.8	100	100	200		0.13	14.5h - 3rd(4d)
	2	in		70.8	47	142	0.8	100	100	200		0.43	3h - 1st
	3	in		71.0	47	147	1.0	100	100	100		0.48	5h - 1st
	4	in		71.1	46	142	1.1	100	100	100		0.34	5h - 1st
37	1	out	f	22.0	45	156	0.8	200	200	200		0.55	14h - 3rd
	2	out		22.0	45	156	0.8	400	200	400		1.08	14h - 3rd
	3	out		22.0	45	156	0.8	400	200	200		0.67	14h - 3rd
	4	out		22.1	44	156	0.7	400	200	200		0.37	14h - 3rd(5d)
	5	out		22.1	46	156	0.7	400	200	200		0.40	15h - 3rd
	6	out		22.2	49	156	0.6	200	200	200		0.33	14h - 3rd(4d)
38	1	out	f	21.5	78	162	1.0	200	200	200		0.38	11h - 3rd
	2	out		21.6	79	162	1.0	200	200	200	200	0.52	11h - 4th(6d)
	3	out		21.6	79	162	1.0	200	200	200	400	0.64	11h - 4th(5d)
	4	out		21.8	79	162	1.1	200	200	200	400	0.72	11h - 4th(6d)
	5	out		21.8	80	162	1.1	400	200	400		0.76	14h - 3rd(5d)
	6	out		21.9	79	162	1.0	400	200	400		0.60	15h - 3rd
	7	out		22.0	78	162	0.9	200	200	200		0.39	14h - 3rd(4d)
39	1	in	f	24.1	45	159	1.0	100	100	100		0.27	13.5h - 3rd
	2	in		24.2	45	159	1.1	200		200		0.51	13.5h - 2nd(3d)
	3	in		24.3	44	159	1.1	100	100	100		0.27	14h - 3rd
40	1	out	f	28.6	55	160	0.9	200	200	200		0.25	13h - 3rd(3d)
	2	out		28.6	55	160	0.9	300	300	300		0.48	15h - 3rd(1d)
	3	out		28.6	55	165	1.0	400	400	400		0.43	15h - 3rd
	4	out		28.7	55	160	1.0	500	500	500		0.66	15.5h - 3rd(5d)
41	1	out	f	2.3	14.1	96	0.4	100	100	100		0.27	14h - 3rd
	2	out		2.3	14.1	96	0.3	100	100	100		0.24	14h - 3rd
	3	out		2.3	14.1	96	0.4	200	100	100		0.31	14h - 3rd(4d)
	4	out		2.3	14.1	96	0.6	200	200	100		0.39	14h - 3rd(1d)
	5	out		2.4	14.1	96	0.7	200	200	100		0.04	14h - 3rd
42	1	in	f	22.7	51	154	0.6	200	200	200		0.15	16h - 3rd
	2	in		23.0	50	154	0.7	200	200	200		0.12	16h - 3rd
	3	out		24.2	49	155	0.8	200	200	200	200	0.57	11h - 4th
	4	out		24.3	48	156	0.8	200	200	200	200	0.77	11h - 4th

	5	out		24.4	52	156	0.8	200	200	200	0.47	15h - 3rd
	6	in		24.6	50	154	0.7	600		200	0.51	12h - 2nd
	7	in		25.2	44	154	0.8	400		400	0.73	16h - 2nd
	8	in		25.6	43	158	0.8	400		400	0.98	16h - 2nd
43	1	out	m	9.9	29	133	0.5	100	100	100	0.27	12h - 3rd(3d)
	2	out		9.9	29	133	0.5	200	200	300	0.54	10h - 3rd(2d)
	3	out		9.9	29	133	0.5	200	200	300	0.76	10h - 3rd(4d)
	4	out		10.0	29	133	0.4	200	200	300	0.50	11h - 3rd
	5	out		10.0	29	133	0.5	200	200	300	0.32	18h - 3rd
	6	out		11.2	31	135	0.6	100	100	100	0.18	12h - 3rd
	7	out		11.4	33	139	0.6	200	200	200	0.29	15.5h - 3rd
44	1	out	m	5.6	16.2	103	0.6	40	30	30	0.05	15h - 3rd(2d)
	2	in		5.7	16.2	103	0.7	100	100	100	0.28	14h - 3rd(3d)
	3	out		5.7	16.2	103	0.5	200	100	200	0.38	15h - 3rd(3d)
	4	out		5.7	16.2	103	0.4	200	200	300	1.42	16h - 3rd(4d)
	5	out		5.7	16.2	103	0.4	200	200	300	0.79	15h - 3rd(4d)
	6	out		5.7	16.2	103	0.6	200	100	200	0.58	14h - 3rd
	7	out		7.7	19.8	115	0.5	100	100	100	0.20	11h - 3rd
45	1	in	m	50.9	80	164	1.0	100	100	100	0.30	2h - 1st
	2	in		52.3	82	160	1.2	200	200	200	0.30	3h - 1st
	3	in		52.4	80	163	1.0	400	400	400	0.47	15h - 3rd
	4	in		52.5	79	163	1.0	300	300	300 300	0.69	16h - 1st
	5	in		52.7	80	163	1.0	400	400	400	0.52	18h - 3rd
	6	in		53.1	73	163	1.0	400	400	400	0.75	12h - 3rd

a) Hospitalized patients and outpatients are designated as in and out, respectively. b) Male and female are designated as m and f, respectively. c) Age in years. In each patient, from the lower to the upper row, data become older. d) Serum creatinine in mg/dl. e) 1st, 2nd, 3rd, and 4th refer to the dose administered at morning, at noon, at evening, and at bed time, respectively. f) Values represent the time (h) elapsed from the last dose and dosing number in a day at sampling. Values in parentheses are the days elapsed from the start of the dosing schedule in the same row, and those for more than 7 d are not shown.

Appendix B. Equations for Predicting Lithium Concentrations

1. Pepin Method substituted with ABW for IBW:

$$CL_{cr} \text{ (for men)} = (140 - \text{age}) ABW / (72 \times S_{cr})$$

$$CL_{cr} \text{ (for women)} = 0.85 \times CL_{cr}$$

$$CL_{cr} \text{ (for children)} = 0.55 \times Ht / S_{cr}$$

$$CL_{Li} = 0.235 \times CL_{cr}$$

$$t_{1/2} = t_{1/2n} / [1 - fu \{1 - (CL_{cr}/100)\}]$$

$$K_e = 0.693 / t_{1/2}$$

$$V_d = CL_{Li} / K_e$$

where

CL_{cr} = estimated creatinine clearance (ml/min)

age = age (years)

S_{cr} = serum creatinine concentration (mg/dl)

ABW = actual body weight (kg)

Ht = height (cm)

CL_{Li} = estimated lithium clearance (ml/min)

$t_{1/2}$ = estimated lithium elimination half-life (h)

$t_{1/2n}$ = population mean half-life (h)

K_e = estimated elimination rate constant (h^{-1})

fu = fraction eliminated unchanged

CL_{cr} in children of less than 15 years was estimated from the formula of Schwartz *et al.* instead of the Cockcroft-Gault equation. In the calculation, fu was set at 0.95 and $t_{1/2n}$ at 24 h.

2. The rearrangement of Zetin equation:

$$C_p = DOSE / 621.5 \\ + 0.458 \times TCA - 0.0113 \times AGE \\ - 0.303 \times SEX - 0.0132 \times WGT - 0.828$$

where

C_p = predicted serum lithium concentration at steady state (meq/l)

$DOSE$ = maintenance dose (mg/day)

AGE = age (year)

WGT = actual body weight (kg)

TCA = 1 for concomitant antidepressant use, 0 for no antidepressant use.

SEX = 1 for male, 0 for female.

The term $FORM$ in original model which is 1 for Lithobid was excluded in this study because this agent was not distributed in Japan.

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