Psychiatry and Clinical Neurosciences (2007), **61**, 269–274 doi:10.1111/j.1440-1819.2007.01654.x

Regular Article

Application of the Cockcroft–Gault method to estimate lithium dosage requirement

CHIH-CHIANG CHIU, MD,[1,2] WINSTON W. SHEN, MD,[1,3] KUN-PO CHEN, MD[2] AND MONG-LIANG LU, MD, MS[3]

[1]*Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei,* [2]*Department of Psychiatry, Songde Branch, Taipei City Hospital, Taipei, and* [3]*Department of Psychiatry, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan*

Abstract The aim of the present study was to assess the precision and bias of a priori methods in the estimation of lithium dosage requirement among bipolar patients. The charts of 82 Diagnostic and Statistical Manual of Mental Disorder–fourth edition bipolar patients with previous history of lithium intoxication were reviewed. After excluding patients who had discontinued lithium treatment, 69 patients were entered to the study. Another 60 bipolar patients without history of lithium intoxication were also included in the study. The demographic data regarding factors thought to affect serum lithium concentrations, including gender, weight, and renal function, was retrospectively collected. Predicted daily lithium doses were calculated by using the new equation derived by the present authors and a priori methods proposed by Pepin *et al.*, Zetin *et al*., Terao *et al.* and Keck *et al*. Mean error was calculated to assess the precision and bias of each a priori method. The Zetin method, the Terao method, and the Keck method had a significant tendency to overpredict dosage requirement. The Pepin method significantly underpredicted dosage. Only the 95% confidence interval of mean error of the present authors' equation was across zero. The present authors' equation represents a precise approach to estimate the lithium dose requirement and is easy to calculate. Regardless of the accuracy of each a priori method in predicting a patient's drug dosage, there is no substitute for proper serum drug concentration monitoring and good clinical judgment. Predictions made by any method should always be assessed clinically before applying its use in a patient.

Key words bipolar disorder, calculation, creatinine clearance, equation, lithium.

INTRODUCTION

Over the past 50 years, lithium has been the agent of choice for the treatment of mood disorders.[1,2] The efficacy of lithium therapy in the treatment of acute mania and long-term prophylaxis against recurrent bipolar disorders is well established.[3–5] Lithium with serum concentrations between 0.6 to 1.2 mEq/L is efficacious in the treatment of bipolar patients.[3–9] Many patients treated with lithium suffer from its adverse reactions.[10] Groleau estimated that 75–90% of patients treated with lithium have signs and symptoms of toxicity at some point during their treatment course.[11] Many mild adverse reactions occur at lithium serum levels of 0.6–1.2 mEq/L, although serious but reversible side-effects can also occur within this range.[12–14] Severe lithium toxic side-effects frequently occur at serum levels above 1.5 mEq/L, and life-threatening side-effects can happen when lithium levels are higher than 2.0 mEq/L.[6–9]

Due to its low therapeutic index, several pharmacokinetic methods have been developed to prospectively determine the lithium dose that will produce a desired steady-state of lithium serum concentration.[15–17] These procedures are to give a lithium test dose first and then measure the post-test dose lithium level. The underlying assumption is that there is a linear relationship between the test dose, the post-test dose lithium

Correspondence address: Mong-Liang Lu, MD, MS, Department of Psychiatry, Taipei Medical University-Wan Fang Hospital, No. 111, Sec. 3, Hsin-Long Road, Taipei 116, Taiwan. Email: mongliang@hotmail.com

Received 19 September 2006; revised 5 January 2007; accepted 6 January 2007.

concentration, the desired steady-state serum lithium concentration, and the lithium maintenance dose. However, these methods carry the risk of undertreatment or toxicity if the initial dosing is in error. For example, the pharmacokinetic techniques such as Cooper *et al.*'s method may lead to potentially toxic lithium dosage.[18]

To lessen these problems, several a priori methods have been developed to predict individual dosage requirement. A priori methods rely on patient-specific values and results of routine laboratory tests to predict individual lithium requirements. Body weight has been used to predict lithium dose in several studies.[19,20] Other a priori methods use mathematical models based on combinations of patient variables to determine lithium dose. The mathematical models include using a first-order, one-compartment pharmacokinetic equation;[21,22] stepwise multiple linear regression;[23,24] and a non-linear mixed-effects model[25] to derive the equation for estimating daily lithium dose.

Lithium is eliminated almost exclusively through the kidneys, where it is filtered through the glomerular membrane and reabsorbed in the proximal tubules. The daily lithium intake and the renal elimination of lithium influence the serum lithium concentration. Lithium clearance varies proportionally with glomerular filtration rate (GFR) and is usually 20–30% of GFR.[26] The inclusion of renal function data, even within normal limits, would ameliorate the predictive accuracy of the a priori equation by Zetin *et al.*[23] because any deviation from the expected values significantly correlated with renal function.[27]

There are several a priori methods including renal function data into equation, such as the Pepin method[22] and the Terao method.[24] Pepin *et al.*[22] predicted the dosage based on an estimate of lithium body clearance. For the Pepin method, the creatinine clearance in mL/min was determined by the Cockcroft–Gault method.[28] The Terao method included four factors (i.e. expected lithium concentration, age, weight, and blood urea nitrogen) into equation to predict the dosage requirement.[24]

One of the shortcomings of many a priori methods for predicting individual dosage requirement is too complicated. They include too many factors into an equation and the coefficients are hard to remember. And the studies were conducted in subjects within normal lithium concentrations. Therefore, the purpose of this study was to derive a simple and accurate equation that predicts the dosage requirement in bipolar subjects with previous history of lithium intoxication. The present authors also compared the new equation with the Keck method,[20] the Zetin method,[23] the Terao method,[24] and the Pepin method.[22]

METHODS

Subjects

The research protocol was approved by the institutional review board. The retrospective study was conducted from July 1999 to June 2003 at Taipei Medical University-Wan Fang Hospital and Songde Branch, Taipei City Hospital, Taipei, Taiwan. In the laboratory of the institutes, the therapeutic serum levels of lithium are set to 0.6–1.2 mEq/L. The staffs in the laboratory automatically notify the treating physicians when their patients' serum lithium levels reach 1.2 mEq/L or more. A total of 82 patients with lithium intoxication (serum lithium level $\geq$ 1.2 mEq/L) were found during the study period. After excluding patients who had discontinued lithium treatment after intoxication or concomitantly used medication influencing lithium level, 69 patients were included. The authors wonder that subjects with previous history of lithium intoxication may have inborn or acquired impairment of lithium clearance. Therefore, the authors collect the data of subjects without previous history of lithium intoxication for comparison. Another 60 patients without the history of lithium intoxication were also included in the present study. Among these, 105 and 24 subjects were sampled during the inpatient and outpatient periods, respectively.

The following data were retrospectively collected: patient's age, gender, height, and bodyweight; diagnosis or indication for the use of lithium; blood urea nitrogen levels; serum creatinine levels; and lithium dosage. Also, adverse reactions were recorded, including lethargy, tremor, delirium, ataxia, polydipsia, and diarrhea.

According to the Diagnostic and Statistical Manual of Mental Disorders–fourth edition (DSM-IV) diagnostic criteria,[29] the main psychiatric diagnosis was bipolar I disorder (121 subjects), major depressive disorder (seven subjects), and schizoaffective disorder (one subject). The demographic characteristics of the patients are summarized in Table 1.

For the 129 study subjects, 34 subjects (26.4%) had lithium-induced adverse reactions. The most common manifestations were tremor (17 cases), lethargy (14 cases), diarrhea (five cases), and polydipsia (four cases).

The equations for lithium dosage prediction

Keck method

The Keck formula[20] is written as follows:

$$\text{Dose (mg/day)} = 20 \times \text{weight}$$

where, weight is total body weight in kilograms.

Table 1. Demographic characteristics of study subjects

	Index group	Control group
Number of patients	69	60
Age	45.3 ± 11.2	39.1 ± 11.7
Gender (M/F)	25/44	21/39
Height (cm)	160.1 ± 12.3	163.3 ± 13.7
Weight (kg)	67.2 ± 14.3	68.9 ± 16.1
Lithium dosage (mg/day)	912 ± 269	897 ± 311
Lithium level (mEq/L)	0.81 ± 0.12	0.79 ± 0.11
Creatinine clearance (mL/min)	87.9 ± 28.9	86.8 ± 29.0

Index group included patients with previous history of lithium intoxication.

Control group included patients without previous history of lithium intoxication.

Zetin method

The stepwise multiple linear regression equation proposed by Zetin *et al*.[23] is as follows:

$$\begin{aligned}\text{Dose (mg/day)} = {} & 486.8 + (746.83 \times \text{level}) - \\ & (10.08 \times \text{age}) + (5.95 \times \text{weight}) + \\ & (92.01 \times \text{status}) + (147.8 \times \text{gender}) - \\ & (74.73 \times \text{tricyclic antidepressant})\end{aligned}$$

where, level is the desired serum lithium concentration in milliequivalents per litre, age is in years, weight is total bodyweight in kilograms, status is 1 for inpatient and 0 for outpatient, gender is 1 for male and 0 for female, and tricyclic antidepressant is 1 for patients receiving concurrent tricyclic antidepressants and 0 for patients not receiving tricyclics.

Terao method

The Terao formula[24] is written as follows:

$$\begin{aligned}&\text{Daily lithium carbonate dose (in milligrams)} = \\ &100.05 + [752.7 \times (\text{expected lithium concentration in millimoles per litre})] - [3.6 \times (\text{age in years})] + [7.2 \times (\text{weight in kilograms})] - [13.7 \times (\text{blood urea nitrogen in milligrams per deciliter})]\end{aligned}$$

Pepin method

The Pepin formula[22] is written as follows:

$$\text{Dose (mmol/day)} = \text{level} \times V_{app} \times \left(1 - e^{-kt}\right) / \left(F \times e^{-kt}\right)$$

where, dose = dosage of lithium in mmol (300 mg lithium carbonate = 8.12 mmol), level = desired steady-state trough concentration in mmol/L, V_{app} = apparent volume of distribution (calculated as Cl_{Li}/K), t = dosage interval (day), F = fraction absorbed (1.0) and $k = 0.693/t_{1/2\_Li}$.

Complimentary formulas to solve Pepin equation include:

To determine ideal weight (kg):

$$\text{For men, weight} = 50 + [90.551 \times (\text{height} - 1.524)]$$

$$\text{For women, weight} = 45.5 + [90.551 \times (\text{height} - 1.524)]$$

To determine clearance of creatinine (mL/min):

$$\text{For men, } Cl_{cr} = [(140\text{-age}) \times \text{weight}] / (72 \times \text{SCr})$$

$$\text{For women, } Cl_{cr} = 0.85 \times [(140\text{-age}) \times \text{weight}] / (72 \times \text{SCr})$$

To determine clearance of lithium (mL/min):

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

To determine $t_{1/2}$ (h):

$$t_{1/2\_Li} = t_{1/2\_n} / \{1\text{-Fe}[1 - (Cl_{cr}/100)]\}$$

where, $t_{1/2\_n}$ = 24 h and Fe = 0.95 (dose excretion).

New equation

The clearance of creatinine (Cl_{cr}) is determined by the Cockcroft–Gault method.[28] The weight is actual bodyweight in kg and SCr means serum creatinine level in mg/dL.

To determine clearance of creatinine (mL/min):

$$\text{For men, } Cl_{cr} = [(140\text{-age}) \times \text{weight}] / (72 \times \text{SCr})$$

$$\text{For women, } Cl_{cr} = 0.85 \times [(140\text{-age}) \times \text{weight}] / (72 \times \text{SCr})$$

The new equation was the following:

$$\begin{aligned}&\text{Daily lithium dose (in milligrams)} = \text{weight} \times 20 \times \\ &(Cl_{cr}/100) \times (\text{expected lithium concentration in millimoles per litre})\end{aligned}$$

The coefficient 20 was derived from the Keck method.[20] And the coefficient 100 was adapted from the normal reference range of creatinine clearance.[30]

Statistical analyses

The dosage calculated by each a priori method was compared with the patient's actual lithium dosage. Values for mean error were calculated for each method to assess precision and bias. The 95% confidence interval was calculated for mean error. The 95% confidence

Table 2. Mean error by prediction method

Method	Index group			Control group		
	Mean error	95% CI	*P*	Mean error	95% CI	*P*
Keck	268.1	205.2–330.0	0.000	267.4	171.9–362.9	0.000
Zetin	108.3	39.2–177.4	0.003	101.5	21.0–182.1	0.016
Terao	251.7	156.7–346.7	0.000	222.9	147.5–298.3	0.000
Pepin	–166.4	–210.1 to –122.7	0.000	–126.0	–189.9 to –102.5	0.000
New equation	–39.6	–124.6 to 45.3	0.353	–90.2	–183.6 to 3.2	0.058

Index group included patients with previous history of lithium intoxication.
Control group included patients without previous history of lithium intoxication.
95% CI, 95% confidence interval.

interval of mean error not containing zero was judged to represent significant bias. A one-way ANOVA with choice of predictive method as the source of variance was performed for absolute mean error data. Post-hoc comparison of mean differences was done with the Scheffé procedure. The predetermined level of significance was 0.05.

RESULTS

Mean error results for predicted dosage by five a priori methods are summarized in Table 2. There were no significant differences in error of lithium dosage estimation between subjects with or without history of lithium intoxication. The Keck method, the Zetin method, and the Terao method significantly overpredicted lithium dosage. The Pepin method significantly underpredicted dosage. The authors' new equation tended to underpredict the lithium dosage requirement, although not significantly.

One-way ANOVA for absolute mean dosage prediction error showed overall significant differences among methods ($P < 0.001$). Pairwise post-hoc comparisons also revealed significant differences ($P = 0.007$ to < 0.001). In post-hoc comparisons, the new equation was significantly more precise than other a priori methods.

DISCUSSION

The authors made a new equation to predict the daily lithium dose requirement to achieve an expected concentration by a statistical method. Compared with other a priori methods, new equation should be considered as the least biased method for predicting lithium dose. With regard to the number of variables, three variables (age, weight, and serum creatinine level) in the new equation were relatively few. The coefficients of these factors were simple and ease to remember. Therefore, the new equation may be simpler and more accurate than other equations, although it is necessary to measure serum creatinine levels before starting lithium treatment.

The direction of prediction error is important to consider. Methods that overpredict, like the Zetin, Terao, and Keck methods, could lead to drug's toxicity. In contrast, a method that significantly underpredicts, such as the Pepin method, could delay achievement of therapeutic serum concentrations and provide less than optimal therapy.

The daily lithium intake and the renal elimination of lithium (lithium clearance) would influence the serum lithium concentration. Several factors might influence the lithium clearance, such as renal function, electrolyte balance, drug–drug interactions, age, bodyweight, gender etc. The Keck method is a weight-based lithium-dosing estimate and may carry the risk of overprediction of lithium dosage requirement.[31] Previous studies reported that the Zetin method could not always accurately predict a required lithium dose and tended to overpredict dose.[24,27,32] Terao *et al*.[24] suggested that the data on renal function should not be neglected. Even if results of the renal function test are within normal limits, the renal function data may be useful, at least partially, to improve the accuracy of the Zetin equation in patients who are old or underweight.[24] Because the authors included serum creatinine level as a variable, its accuracy was substantially improved over that of the Zetin method. Although the Terao method included blood urea nitrogen levels in the equation, it also overpredicted the lithium dose in the present study. The serum creatinine level is less influenced by extra-renal factors than is the blood urea nitrogen level, and is the more accurate test.[33] This factor might partially contribute to the biased estimation in the Terao method. The present study confirms previous reports that the Pepin method underpredicts dosage.[32,34] Dugas and Feeney[35] proposed a compound effect of gender and weight correction factors in the equation. Substitution of actual

weight for lean weight improved their prediction accuracy.[35] In the present sample, similar substitution had also improved the prediction accuracy.

Vigorous treatment, aimed at achieving symptom control as promptly as possible while avoiding adverse effects, is important. Goldberg *et al*.[36] reported that regardless of mood-stabilizer the speed to reach therapeutic serum concentrations significantly affects time to remission. Therefore, the exact dose predicting regimen that brings mood symptoms under control is likely to reduce the risks of adverse effects, optimize functional status, and reduce eventual poor compliance.

Potential limitations to generalization of the present results must be considered. First, the sample size of the present study was small. Second, the authors' data were collected retrospectively. Potential biases, such as the treatment compliance, the timing of blood sampling, and concurrent treatment, were difficult to assess. Therefore, larger prospective studies are needed to verify the accuracy of the new equation.

Despite these limitations, the authors' equation represents a novel approach to estimate the lithium dose requirement and is easy to calculate. The authors believe that the costs of prolonged hospitalization because of subtherapeutic dosing and the risks of clinical toxicity due to give excessive doses may be decreased by the use of an appropriate dose-estimation method at the beginning of lithium therapy. Regardless of the accuracy of an a priori method in predicting a patient's drug dosage, there is no substitute for proper serum drug concentration monitoring and good clinical judgment. Predictions made by any method should always be assessed clinically before applying its use in a patient.

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