A Retrospective Study of Three Lithium Dose and Serum Concentration Prediction Methods

J. Rivington, B. Corrigan, K. McKenna and F. Jamali

ABSTRACT

The performance of various lithium dose and serum concentration prediction methods in an inpatient setting was assessed using a retrospective chart review of 50 patients with bipolar affective disorder. Only three predictive methods could actually be applied in this setting. Regression of predicted versus actual dose and predicted versus observed serum concentration for Jermain et al's, Pepin et al's, and Zetin et al's methods yielded r values of 0.594, 0.255, and 0.654, respectively. The method of Zetin et al produced the most powerful prediction, least bias and greatest precision. This method is feasible in most settings for dose prediction.

Key Words: *Dose Prediction, Lithium, Pharmacokinetics.*

RÉSUMÉ

L'efficacité de diverses méthodes de prédiction de la dose et des concentrations plasmatiques de lithium a été évaluée en milieu hospitalier à partir de la revue rétrospective des schémas posologiques de 50 patients atteints de troubles affectifs bipolaires. Trois méthodes prédictives seulement ont pu être utilisées dans ce contexte. Les valeurs de régression obtenues à partir des méthodes de Jermain et ses collègues, de Pepin et coll. et de Zetin et coll., pour la dose prédite à la dose réelle et les concentrations plasmatiques prédites aux concentrations plasmatiques observées étaient respectivement les suivantes : r = 0,594, r = 0,255 et r = 0,654. La méthode de Zetin et coll. a permis d'obtenir les prédictions à la fois les plus remarquables et précises, et les moins biaisées. Cette méthode de prédiction de la dose peut être utilisée dans la plupart des contextes.

Mots clés : *lithium, pharmacocinétique, prédiction de la dose,*

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INTRODUCTION

Lithium is the primary treatment for long-term therapy of recurrent bipolar affective disorders.[1] The main limitation to the use of lithium is its toxicity characterized by its narrow therapeutic window, and wide interpatient variability. As a result, the use of lithium requires adequate pharmacokinetic monitoring to ensure therapeutic effect and to limit toxicity.[2]

There have been several methods developed including population based modeling for predicting appropriate lithium dose for patients.[3-11] However, many of these methods have been developed under well controlled conditions, or in established clinical pharmacokinetic settings. The utility of these methods in a regular hospital setting by individuals with a limited background in kinetics and outside of established kinetic monitoring programs has not been examined.

The purpose of this study was to identify a method for predicting appropriate lithium doses which can be implemented in outpatient settings or in hospital where there is no established therapeutic drug monitoring program.

METHOD

The study was approved by the Human Ethics Committee of the Grey Nuns Hospital (Edmonton, Alberta). It involved a retrospective chart review of 50 patients with bipolar disorder treated with lithium (18 males and 32 females) admitted to the Grey Nuns Hospital. The data collected which were relevant to application of lithium pharmacokinetic equations included, date of birth, gender, total body weight, serum creatinine, lithium dose, lithium brand, steady state lithium levels, sample collection time, and concurrent medications.

Various methods[3-11] were considered for application in this study. Due to the retrospective nature of the research plan; however, only those of Zetin et al[3], Pepin et al[4], and Jermain et al[5] were found useful for this purpose. The equations used can be found in Appendix A.

Predicted doses were plotted versus the actual administered doses. In addition, the equations were rearranged for calculation of predicted concentration. The association between the predicted and administered doses and between the observed concentrations were assessed using linear regression. Precision was

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calculated as the square root of the mean squared error between actual and observed values expressed as percent (RMSE%). Bias was calculated as the mean error between actual and observed values, expressed as percent (MPE).

RESULTS AND DISCUSSION

Table I describes the patient population under study. Of the initial sample population (n=50), three were excluded in Pepin et al's and Jermain et al's method due to lack of reported serum creatinine in charts. All necessary data were available for the analysis of Zetin et al's equations.

Table II depicts the relative precision and bias of the observed serum levels and administered doses. The method of Zetin et al[3] proved most precise (RMSE of 26.8% and 35.1% for dose and concentration, respectively) with the least amount of bias (Mean percent error of 15.7% and 9.6% of concentration and dose, respectively). The association between predicted and observed values were significant ($p<0.05$) for all methods used except for the Pepin dose prediction ($p<0.083$). The Zetin method also exhibited the strongest coefficient of correlation for dose ($r=0.654$). In general, stronger correlations were found between doses as compared with serum concentrations. The reason for the difference in r values between dose and concentration was due to the fact that doses were limited by the current dosage availability (usually multiples of 150 mg) while concentrations did not have this limitation. The dose correlations are shown in Figure 1.

There are many practical limitations to the implementation of lithium pharmacokinetic monitoring. The steady-state concentration term in equations 1-3 (*Css*) refers to that predicted at 12 hours post-dose, although the time the concentrations were actually measured varied from 10 to 15 hours post-dose. This reflects a restriction imposed by hospital routine and is an important consideration in the evaluation of these equations. There is generally a lack of trained staff, lack of funds, and lack of coordination between pharmacy staff and those collecting samples. All of these factors tend to keep many centres from implementing lithium monitoring programs. Hence, dose prediction methods are essential. For such methods to be clinically useful, they must be reasonably accurate, be easy to use, and the data required must be attained quickly and easily in a cost effective manner.

Many of the methods currently available are data intensive and are not practical for routine use. The method of Perry et al[7,8] and the method of Swartz et al[10] require two serum concentrations be taken after a single dose which represent different parts of the concentration time curve to estimate the elimination rate constant. This limits the application of these methods due to the increased work involved and lack of cost effectiveness. Norman's predictive method which is based on renal lithium clearance requires a urine collection.[9] Urine collections lack practicality in mentally unstable patients. For our purpose, the nomogram developed by Cooper et al[6], was not suitable for our retrospective studies since it is based on a 24-hour serum lithium level after an initial 600 mg dose. There is equally a reluctance to use computer based systems due to the cost involved in purchasing and upgrading software, their difficulty of use, availability in a ward setting, and reluctance to apply values when the method by which they are obtained is not understood by the clinician.

The advantage of the methods proposed by Zetin et al[3], Pepin et al[4], and Jermain et al[5] over other methods is that the dose can be predicted based on very limited information, and for dose prediction no serum concentration measurement is required. Of the methods tested, Zetin et al's[3] appeared to be most suitable and reliable as predicted concentrations were reasonably accurate and precise. All the data required for its use were readily available to clinicians by direct

Table I: Description of variables used in the study

	Mean ± S.D.	Range
Age (years)	39.8 ± 15.0	15 – 70
Total Body Weight (kg)	73.4 ± 18.8	47 – 124
Serum Creatinine (μmol/L)	80.0 ± 24.4	43 – 185
Lithium dose (mg)	1101 ± 360	300 – 2400
Lithium Level (mEq/L)	0.73 ± 0.20	0.31 – 1.11
Collection Time (hours) (Post dose)	13.2 ± 1.6	10 – 15

Table II: Precision (Root Mean Squared Error in percent (RMSE)) and Bias (Mean Percent Error (MPE)) of prediction of serum concentration and dose using methods of Jermain et al (J), Pepin et al (P) and Zetin et al (Z).

	Concentrations			Doses		
Mean Percent Error	J	P	Z	J	P	Z
RMSE (%)	58.0	51.5	35.1	38.6	44.5	26.8
MPE(%)	50.5	37.1	9.5	-36.7	12.5	15.7

history, or from chart review. The calculations required are simple, easy to understand, and can be done immediately on site. However, the methods proposed here are designed to predict the dose and are not replacement for routine monitoring of the treatment. Even though the Zetin method proved most reliable, due to the relatively large degree of variability in the disposition kinetics of lithium, we recommend periodic serum concentration measurements after the dose is predicted based upon the method of Zetin et al[3].

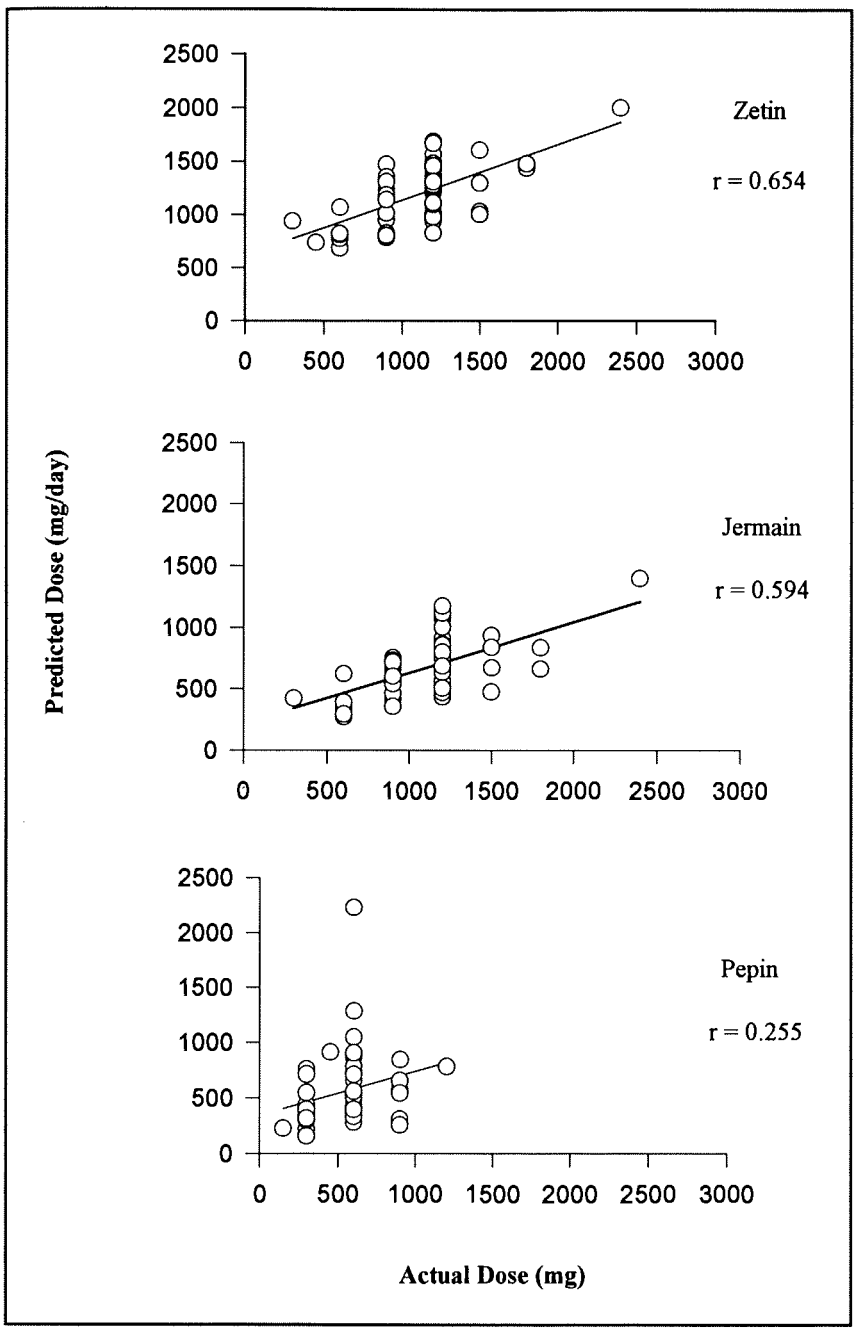

Figure I: Predicted dose versus actual dose for methods of Zetin et al, Jermain et al, and Pepin et al.

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Appendix A

Equation 1, Zetin et al[3]

$$Dose_{pr} = 486.6 + 746.83Css - 10.08age + 5.95TBW + 92.01status + 147.8sex - 74.73TCA$$

Where $Dose_{pr}$ is the predicted total daily dose of lithium in mg; Css is the actual 12 hour steady-state concentration in mmol/L; age is in years; TBW is the total body weight in kg; $status$, constants of 1 for inpatient and 0 for outpatients; sex, constants of 1 for male and 0 for female; TCA constants of 1 for concomitant use of tricyclic antidepressants and 0 for no concomitant use of tricyclic antidepressants.

Equation 2, Pepin et al[4]

$$C_{ss} = \frac{F \cdot dose \cdot e^{-k\tau}}{V(1 - e^{-k\tau})}$$

Where F is the fraction of the dose absorbed (assumed to be 1); $dose$ is the actual given dose; k is the estimated elimination rate constant calculated from

$$k(hr^{-1}) = \frac{0.693}{24hr \Big/ \left[1 - 0.95\left(1 - \frac{CLCr(mL/\text{min})}{100}\right)\right]}$$

where τ is the dosing time interval, V is the volume of distribution calculated from $u = CLLi//k$, and $CLLi$ is lithium clearance calculated from

$$CLLi = CLCr(L/h) \cdot 0.235.$$

Equation 3, Jermain et al[5]

$$C_{ss} = \frac{dose\ (mmol/day)}{CLLi\ (L/day)}$$

Where $CLLi = [0.093 \cdot LBW] + [0.0885 \cdot \text{CLCr}(L/h)]$.

Where applied, $CLCr$ is creatinine clearance determined over 24 hours.

Correction

Please be advised that Equation 2 in Appendix A of article *A Retrospective Study of Three Lithium Dose and Serum Concentration Prediction Methods* from the August 1995 issue was printed incorrectly. The correct equation is printed below. Please accept our apologies for any inconvenience this may have caused.

Equation 2, Pepin et al[4]

$$C_{ss} = \frac{F \cdot dose \cdot e^{-k\tau}}{V(1 - e^{-k\tau})}$$

Where F is the fraction of the dose absorbed (assumed to be 1); *dose* is the actual given dose; k is the estimated elimination rate constant calculated from

$$k(hr^{-1}) = \frac{0.693}{24hr \Big/ \left[1 - 0.95\left(\frac{1 - CLCr(mL/\text{min})}{100}\right)\right]}$$

where τ is the dosing time interval, V is the volume of distribution calculated from $V = CLLi//k$, and $CLLi$ is lithium clearance calculated from

$$CLLi = CLCr(L/h) \cdot 0.235.$$