British Journal of Psychiatry (1986), **148**, 401–405

The Utility of a Single-Point Dosing Protocol for Predicting Steady-State Lithium Levels

PAUL J. PERRY, BRUCE ALEXANDER, RANDALL A. PRINCE AND FREDERICK J. DUNNER

Two methods for predicting steady-state serum lithium level were compared prospectively in in-patients suffering from affective disorder. A single-point prospective administration model that required a single 24-hour serum lithium level, following a test dose produced statistically similar predictions of the observed steady-state lithium levels as did a model that required 12- and 36-hour levels. However, the latter two-point method produced significantly more accurate predictions from clinical interpretation. Although the two-point approach is preferable, the single-point method is clinically acceptable if its limitations of accuracy are taken into consideration.

Cooper *et al* (1973) described the first prospective method for administering lithium, which recommended a daily maintenance dose that would produce a steady-state lithium concentration between 0.6 and 1.2 mEq/l; the only information required was a 24-hour serum lithium level following a 600 mg lithium carbonate test dose. Gengo *et al* (1980) reported that this procedure was accurate in 96% of 24 patients. However, Naiman *et al* (1981), using the same procedure, found that only nine out of 13 patients were within the range; Perry *et al.* (1983), noting these discrepancies, confirmed that the method was successful, and calculated two new administration schedules. The first predicted the lithium carbonate maintenance dose required for the prophylactic treatment of affective illness, while the second predicted the ideal maintenance dose for the treatment of manic episodes. In a subsequent study, Perry *et al* (1984) prospectively tested these two schedules: out of 18 patients who required prophylactic lithium levels between 0.40 and 0.89 mEq/l, the maintenance dose achieved the pre-defined therapeutic range in 15 (83%); out of 20 patients requiring lithium concentrations between 0.90 and 1.30 mEq/l for the treatment of manic episodes, 17 (85%) attained the therapeutic range after receiving the recommended maintenance dose. Despite these findings, the accuracy and sensitivity of single-point methods have been questioned, compared to the multiple-point prediction method Perry *et al* (1982). However, no controlled comparative studies have actually compared the accuracy and sensitivity of these two different approaches to prospective lithium administration.

It was our objective to determine whether steady-state serum lithium levels could be predicted with similar accuracy, utilising a single-point predictive method, as opposed to the multiple-point.

Method

Forty-seven adult patients requiring lithium for the treatment of their affective illness and who had been admitted to the psychiatric service of two university-affiliated hospitals, participated. Exclusion criteria included significant renal, hepatic, or cardiovascular disease, as well as mental retardation or committment by courts. No patients had fluctuating renal function or were on salt-restricted diets; all had their history taken on admission, and received a physical and laboratory examination that included blood, electrolytes, and thyroid function. The patients were maintained on a regular hospital diet with unrestricted fluid intake, and could receive either antipsychotic or antidepressant drugs. Patients receiving diuretics were required to have been stabilised on them for more than a month before entry.

Each patient received a 1200 mg test dose of lithium carbonate at approximately 8 p.m; serum lithium samples were obtained by intravenous puncture at 12, 24, and 36 hours following the test dose. A final steady-state serum lithium level was drawn at a time greater than five-times the estimated serum lithium half-life, following the administration of a fixed maintenance dose. Patients receiving lithium prophylactically were started on a maintenance dose that was predicted to achieve a therapeutic serum lithium concentration between 0.4 and 0.89 mEq/l, while those receiving lithium for mania received a dose predicted to achieve a therapeutic level between 0.9 and 1.3 mEq/l.

The serum lithium concentration between 0.4 and 0.89 mEq/l, while those receiving lithium for mania received a dose predicted to achieve a therapeutic level between 0.9 and 1.3 mEq/l.

The serum lithium concentrations were analysed spectrophotometrically (Hansen, 1968); the levels analysed at the

Psychiatric Hospital and the VA Medical Center had coefficients of variation of 1.6% and 2.9% respectively.

To predict the lithium dose necessary for the patient's plasma levels to fall within the therapeutic range, a standard pharmacokinetic method was employed (Gibaldi & Perrier, 1975). The validity of using this prospective dosing technique for predicting steady-state serum lithium concentrations has been described elsewhere (Perry *et al*, 1982).

A mathematical relationship has been described between drug concentration in serum or plasma at steady-state and a single drug concentration at some time after a test dose (Slattery *et al* 1980). The derivation suggests that a reciprocal relationship exists between the maintenance dose and test dose drug concentration, whereas there is a direct proportional relationship between the mean steady-state drug concentration and the test dose drug concentration. To examine this linear relationship, the steady-state serum lithium concentrations at 12 hours following the dose were standardised to a maintenance dose of 1800 mg per day. The normalised steady-state serum lithium concentrations were then subjected to linear regression analysis against the test dose serum lithium concentrations observed at 12-, 24-, and 36- hours. The linear regression equations and correlation coefficients were determined individually for the 12-, 24-, and 36- hour test dose points. Seventeen patients were subjected to this analysis for the 12- and 24-hour test dose serum lithium concentration, while 15 patients had the same analysis at 36 hours. Thus, the preliminary analysis defined the linear relationships between a 1200 mg lithium carbonate test dose, with its resulting 12-, 24-, and 36-hour serum lithium concentrations, and the corresponding steady-state serum lithium concentration for an 1800 mg per day maintenance dose.

Following the derivation of these three linear relationships, 30 patients prospectively had their doses changed so that the appropriate therapeutic range was achieved, utilising the multiple-point prediction protocol for predicting serum lithium levels (Perry, 1982). Only the 12- and 36-hour test dose lithium concentrations were utilised in these calculations. Steady-state serum lithium concentrations for the three single-point equations were calculated by substituting the respective 12-, 24-, or 36-hour serum lithium levels into the respective equations, and then proportionally adjusting the steady-state concentration to the administered lithium carbonate maintenance dose. For example, if the single-point equation predicted a steady-state level of 1.0 mEq/l, this indicated the steady-state level for a 1800 mg per day lithium carbonate maintenance dose. Thus, a 1200 mg per day maintenance dose would yield a 0.67 mEq/l steady-state serum lithium concentration, a 2400 mg per day dose would predict a 1.33 mEq/l steady-state level, etc.

The steady-state serum lithium concentrations predicted by the single-point equations and the multiple-point equation were compared to the observed steady-state serum lithium concentrations, utilising multivariate analysis of variance. A significance level of 5% was assumed for all tests. In cases where the F ratio was found to be significant, the t-test for multiple comparisons was used to determine which means differed significantly. The precision and bias of the predictive methods were estimated by measuring the mean squared error and mean error respectively (Sheiner, 1981).

TABLE I

Observed and standardised steady-state serum lithium concentrations

Patient	*Lithium maintenance dose (mg per day)*	*Observed steady-state serum lithium level (mEq/l)*	*Standardised steady-state serum lithium level* (mEq/l)*
1	1200	0.68	1.02
2	900	0.41	0.82
3	1200	0.66	0.99
4	1200	0.57	0.86
5	1500	0.88	1.06
6	1800	0.74	0.74
7	2100	0.79	0.68
8	2400	0.88	0.66
9	1200	0.84	1.26
10	1800	1.27	1.27
11	1800	1.15	1.15
12	1500	1.09	1.31
13	2400	1.00	0.75
14	1500	1.17	1.40
15	1800	0.90	0.90
16	1800	1.03	1.03
17	2400	1.01	0.76

*The steady-state lithium concentrations were standardised to a 1800 mg per day maintenance dose.

TABLE II

Regression equations for standardised steady-state serum lithium concentration versus post-test dose serum lithium concentrations

Hours after test dose	*Linear regression equation**	*r*	*n*	*P*
12	$C^{ss}_{12h} = 0.182 + 1.62$ (Se Li)	0.56	17	<0.05
24	$C^{ss}_{12h} = 0.131 + 3.29$ (Se Li)	0.79	17	<0.001
36	$C^{ss}_{12h} = 0.216 + 3.95$ (Se Li)	0.95	15†	<0.001

*C^{ss}_{12h} is the steady-state serum lithium concentration for a 1800 mg per day maintenance dose; Se Li is the serum lithium concentration at either 12, 24 and 36 hours following a 1200 mg test dose for the respective equations.

†Only 15 36-hour serum lithium levels were available for the 17 patients studied.

TABLE III
Performance evaluation of four predictors

	Observed	*Steady-state lithium concentrations (mEq/l)*			*Two-point method*
		Single-point method			
		12-hour prediction	*24-hour prediction*	*36-hour prediction*	
Mean (SD)	0.97 (0.22)	0.82 (0.21)	0.91 (0.22)	0.88 (0.22)	0.92 (0.25)
Mean squared error $(mEq/l)^2$		0.054	0.026	0.034	0.029
Mean error		−0.143	−0.053	−0.090	−0.047

Results

Following the administration of the 1200 mg lithium carbonate test dose, the first 17 patients received maintenance doses suitable for treating manic patients or patients requiring prophylactic lithium for their affective illness; their serum lithium levels ranged from 0.41 to 1.27 mEq/l for maintenance doses that ranged from 900 to 2400 mg per day (Table I). The three linear regression equations that tested the relationship between the standardised steady-state serum lithium concentrations and the post-test dose serum levels at 12-, 24-, and 36-hours are given in Table II; these three predictive equations were prospectively tested in an additional 30 patients.

The observed mean steady-state serum lithium level of 0.97 ± 0.22 mEq/l differed significantly ($F = 18.06$, $P < 0.001$) from the 12-hour point equation prediction of 0.82 ± 0.21 mEq/l and from the mean 36-hour point prediction of 0.88 ± 0.22 mEq/l ($F = 8.76$, $P < 0.01$). However, the 24-hour single-point equation and the two-point method predictions were similar to the observed levels. The single-point 24-hour predictive equation's mean steady-state lithium level of 0.91 ± 0.22 mEq/L ($F = 3.46$, $P = 0.07$) and the two-point method's mean level of 0.92 ± 0.25 ($F = 2.37$, $P = 0.14$) were not significantly different than the observed mean steady-state serum lithium concentration. An evaluation of the absolute performance of the predictions is presented in Table III. The mean squared error (a measure of precision) and the mean error (a measure of bias) are nearly identical for the single-point 24-hour equation predictions, and the two-point method's predictions thereby confirmed the findings of the multiple analysis of variance.

Discussion

These results indicate that the single-point prospective administration model that requires a 24-hour serum lithium level following a 1200 mg lithium carbonate test dose yielded statistically similar predictions to the observed steady-state serum lithium concentrations, as did the two-point prospective dosing model. However, despite the statistical similarity between the two-point predictive method and the 24-hour one-point predictive method, the results are deceiving. Perry *et al* (1982) defined clinical acceptability for the predictive level in their pharmacokinetic dosing protocol for lithium as a steady-state serum lithium concentration within 0.1 mEq/l of the observed level. Application of this criterion to these data suggests that the two-point predictive method is clinically superior to the one-point. By utilising the two-point method to calculate the steady-state lithium levels in 30 patients, 77% of the predictions fell within the 0.1 mEq/l clinical acceptability range, but the single-point predictive equations did not fare nearly as well. The 12-hour equation yielded a 40% acceptability rate, while the 24-hour and the 36-hour equations produced 43% and 60% rates respectively. A significant difference is obvious between the two-point method prediction and the 24-hour single-point prediction ($\chi^2 = 6.94$, $P < 0.05$).

However, if the clinical acceptability criterion is extended to a range of ± 0.15 mEq/l, the rates are considerably different. The acceptability rates were 80% for the two-point method, 73% for the 24-hour equation, 70% for the 36-hour equation, and 53% for the 12-hour equation. Thus, the statistical precision of the two-point method and 24-hour equation are similar, but the methods differ considerably in their clinical usefulness. The two-point method is clearly a more accurate predictor of steady-state lithium levels. If the clinician intends to use the 24-hour single-point method, he must be willing to accept a lower degree of accuracy.

The advantages of the two-point method include the flexibility of the sampling times and knowledge of the individual lithium elimination half-life; lithium levels can be drawn at times convenient to the patient and clinician, as long as a 24-hour time-span exists between the two samples. This requirement is an absolute necessity because of the

diurnal variation in lithium clearance (Lauritsen *et al*, 1981). Estimation of the lithium half-life over a shorter time-span than 24 hours has been demonstrated to produce significant inaccuracies in the steady-state predictions (Perry *et al* 1982). Knowing the lithium half-life in a patient results in two clinical advantages. Firstly, if the lithium half-life is excessively long, i.e. >30 hours, the clinician is alerted to the need to monitor renal function more closely while the patient is receiving lithium, because of lithium's potential risk as a nephrotoxin (Perry, 1982). The second advantage is evident in the patient where a relatively short lithium half-life, i.e. <15 hours is found. The most obvious explanation for errors in the lithium prediction is related indirectly to the lithium half-life and directly to the lithium clearance. The mean lithium half-life for the 30 prospectively dosed patients was 21.2 ± 6.6 hours; it appears that the patients whose predictions were outside the clinical acceptability range were often those where the drugs half-life was <15- or >30 hours. The explanation for this error in prediction is probably related to the diurnal variation in lithium clearance: Lauritsen *et al* (1981) found nocturnal lithium clearances to be 22% less than daytime ones. The mechanism for diurnal variation in lithium clearance is a direct result of the glomerular filtration rate being significantly lower at night, when the patient is supine, and elevated during the day, when the patient is standing. The primary source of error in prospective dosing methods for lithium results from dynamic changes in the glomerular filtration rate, originating from changes in hyperactivity of the manic patient. If the lithium test dose is administered when the patient is in a hyperactive state, e.g. when sleeping and supine for only two hours at night, and the 12-hour steady-state sample is measured a week later, when the patient is not hyperactive, e.g. sleeping and supine for eight hours a night, a higher than predicted steady-state lithium level will be observed. The reverse situation may also occur. The half-life data partially support this hypothesis: in the seven cases where the two-point predictions were not clinically acceptable, the half-lives were either >30 or <15 hours in 43% (3/7) of the cases for the two-point method and 42% (7/17) of the 24-hour single-point method. The only disadvantage of the two point-method is that the use of a hand-held calculator or microcomputer is required. (A program listing for the Apple 2E or IBM PC computer is available from the authors.)

The disadvantages of the single-point equations are the disregard of the lithium half-lives in individual patients and inflexibility of the sampling times. Since the half-life is unknown, it is probably not reasonable to draw a steady-state level until at least eight days after starting the maintenance schedule. This recommendation is based upon the fact that in the prospective population of 30 patients, the lithium half-life values ranged for 9.5 to 36.8 hours. The serum sampling problem is troublesome if the 24-hour single-point sample or the 12-hour steady-state sample is inadvertently missed, because there is no alternative procedure.

The advantage of the single-point method is its inherent simplicity; a lithium dosing nomogram has been constructed for the single-point dosing protocol. However, we do not recommend using the nomogram except in outpatients requiring prophylactic serum lithium concentrations in the range of 0.4–0.6 mEq/l (Hullin, 1979). This precaution stems from our experience with one patient in whom an 1800 mg per day maintenance dose produced a steady-state level of 1.17 mEq/l, while the nomogram based on the 24-hour serum lithium level following the test dose predicted a steady-state level of 0.79 mEq/l. The multiple-point method cautioned us in advance to prescribe lithium cautiously because of the 12-hour half-life. However, had a clinician been prescribing for a manic patient with only the dosing nomogram, there is a reasonable probability that the patient could have experienced toxic serum lithium levels with less cautious administration. Thus, we have put an upper steady-state limit of 0.9 mEq/l on the lithium dosing nomogram. (The lithium dosing nomogram suitable for prophylactic prospective dosing is available from the authors upon request).

These findings suggest that the two-point method is preferable for the prescription of lithium in acutely ill patients with affective illness. Much of the unpredictability of the methods can probably be explained by variability in patients' lithium clearances between the time of administering the test dose and obtaining the steady-state serum lithium level. Since only the two-point method allows one to suspect this potential problem in advance, because of knowledge of the lithium half-life, we prefer the use of the two-point method. As initially hypothesised, the two-point method, because of its greater accuracy, is also clinically superior in its steady-state lithium predictions than the 24-hour single-point method. However, the latter method can be used clinically in outpatients requiring prophylactic lithium levels, if the clinician is willing to accept the lesser degree of accuracy for the simplicity of the predictive method requiring only a single blood level, drawn at 24 hours after the test dose.

References

CALDWELL, H. C., WESTLAKE, W. J., CONNER, S. M. & FLANAGAN, T. (1971) A pharmacokinetic analysis of lithium carbonate absorption from several formulations in man. *Journal of Clinical Pharmacology*, **11**, 349–56.

COOPER, T. B., BERGNER, P. E. E. & SIMPSON, G. M. (1973) The 24-hour serum lithium level as a prognosticator of dosage requirements. *American Journal of Psychiatry*, **130**, 601–3.

GENGO, F., TIMKO, J., D'ANTONIO, J., RAMSEY, T. A., FRAZER, A. & MENDELS, J. (1980) Prediction of dosage of lithium carbonate: use of a standard predictive method. *Journal of Clinical Psychiatry*, **41**, 319–21.

GIBALDI, M. & PERRIER, D. (1975) *Pharmacokinetics*, New York: Marcel Dekker.

HANSEN, J. L. (1968) The measurement of serum and urine lithium by atomic absorption spectrophotometry. *American Journal of Medical Technology*, **34**, 625–33.

HULLIN, R. P. (1979). Minimum effective plasma lithium levels for long-term preventive treatment of recurrent affective disorders. In *Lithium: Controversies and Unresolved Issues*. (Cooper T. B., Gershon S., Kline N. S., *et al*, eds). Amsterdam: Excerpta Medica.

LAURITSEN, B. J., MELLERUP, E. T., PLENGE, P., RASMUSSEN, S., VESTERGAARD, P. & SCHOU M. (1981). Serum lithium concentrations around the clock with different treatment regimens and the diurnal variation of the renal lithium clearance. *Acta Psychiactrica Scandinavica*, **64**, 314–9.

NAIMAN, I. F., MUNIZ, C. E., STEWART, R. B. & YOST, R. L. (1981) Practicality of a lithium dosing guide. *American Journal of Psychiatry*, **138**, 1369–71.

PERRY, P. J. (1982). Lithium nephrotoxicity. *Drug Intelligence and Clinical Pharmacy*, **16**, 740–4.

PERRY, P. J., ALEXANDER, B., DUNNER, F. J., SCHOENWALD, R. D., PFOHL, B, & MILLER, D. (1982) Pharmacokinetic protocol for predicting serum lithium levels. *Journal of Clinical Psychopharmacology*, **2**, 114–8.

——, PRINCE, R. A., ALEXANDER, B. & DUNNER, F. J. (1983) Prediction of lithium maintenance doses using a single point prediction protocol. *Journal of Clinical Psychopharmacology*, **3**, 13–7.

——, ALEXANDER, B., PRINCE, R. A. & DUNNER, F. J. (1984) Prospective evaluation of two lithium maintenance dose schedules. *Journal of Clinical Psychopharmacology*, **4**, 242–46.

SHEINER, L. B. & BEAL, S. L. (1981) Some suggestions for measuring predictive performance. *J. Pharmacokinet Biopharm*, **9**, 503–512.

SLATTERY, J. C., GIBALDI, M. & KOUP, J. R. (1980) Prediction of maintenance dose required to attain a desired drug concentration at a steady state from a single determination of concentration after an initial dose. *Clinical Pharmacokinetics*, **5**, 377–85.

*P. J. Perry, PhD, *Associate Professor of Clinical Pharmacy*.

B. Alexander, Pharm D, *Clinical Associate Professor of Clinical Pharmacy*.

R. A. Prince, Pharm D, *Associate Professor of Clinical Pharmacy*.

F. J. Dunner, MD, *Clinical Assistant Professor of Psychiatry, University of Iowa, Iowa City. IA52242, USA*.

*Correspondence

(*Accepted 27 December 1984*)