

# Accuracy of the Pepin method to determine appropriate lithium dosages in healthy volunteers

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**Objective:** To assess if the lithium dosage prescribed according to the Pepin method leads to therapeutic serum concentrations of lithium. **Methods:** For 13 healthy volunteers, the initial daily doses of lithium were calculated according to the Pepin formula with a view to obtaining a serum lithium level of 0.8 mmol/L. Lithium was administered twice daily for 21 days, and blood samples were drawn daily, 12 hours after the last dose was taken. Dosage was adjusted if serum concentrations were below 0.6 mmol/L or above 1.0 mmol/L or if major side effects were reported. **Results:** Daily lithium doses ranged from 1050 mg to 1950 mg (mean 1569 mg, standard deviation [SD] 291 mg). The mean serum lithium concentrations for weeks 1, 2 and 3 were 0.74 mmol/L (SD 0.19 mmol/L), 0.67 mmol/L (SD 0.22 mmol/L) and 0.69 mmol/L (SD 0.13 mmol/L), respectively. Within-subject variance was negligible. Sixty-eight percent of the serum lithium concentration measurements fell between 0.57 mmol/L and 0.83 mmol/L, and 84% fell within the recommended therapeutic range of 0.60 mmol/L and 1.20 mmol/L. **Conclusions:** The Pepin method is a safe but conservative method for predicting the appropriate daily dose of lithium.

**Objectif :** Déterminer si la dose de lithium prescrite selon la méthode Pepin produit des concentrations thérapeutiques de lithium dans le sérum. **Méthodes :** Chez 13 volontaires en bonne santé, on a calculé les doses quotidiennes initiales de lithium en fonction de la formule Pepin afin d'obtenir des taux de 0,8 mmol/L de lithium dans le sérum. Le lithium a été administré deux fois par jour pendant 21 jours et l'on a prélevé des échantillons de sang tous les jours, 12 heures après la dernière dose. On a rajusté la posologie si les taux sériques tombaient à moins de 0,6 mmol/L ou dépassaient 1,0 mmol/L, ou si l'on signalait des effets secondaires importants. **Résultats :** Les doses quotidiennes de lithium ont varié de 1050 mg à 1950 mg (moyenne de 1569 mg, écart type [ET] de 291 mg). Les concentrations moyennes de lithium dans le sérum au cours des semaines 1, 2 et 3 se sont établies à 0,74 mmol/L (ET, 0,19 mmol/L), 0,67 mmol/L (ET, 0,22 mmol/L) et 0,69 mmol/L (ET, 0,13 mmol/L) respectivement. L'écart chez un même sujet a été négligeable. Soixante-huit pour cent des mesures de concentration du lithium dans le sérum

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ont varié de 0,57 mmol/L à 0,83 mmol/L et 84 % se sont établies à l'intérieur de la plage thérapeutique recommandée de 0,60 mmol/L à 1,20 mmol/L. **Conclusions :** La méthode Pepin est une façon sécuritaire mais conservatrice de calculer la bonne dose quotidienne de lithium.

## Introduction

At the beginning of bipolar patients' treatment with lithium, it is often necessary to adjust the dosage as fast as possible. The recommended serum level to obtain a beneficial effect in bipolar disorder is between 0.60 mmol/L and 1.20 mmol/L.<sup>12</sup> Inappropriate dosage can entail a poor control of symptoms and potentially dangerous side effects.<sup>3</sup> Thus, predicting the optimal dosage to obtain optimal therapeutic concentration is important. An individualized approach to drug dosage is therefore necessary for the safe and effective use of lithium medication. It has been shown that pharmacokinetic techniques such as Cooper's method may lead to potentially toxic lithium dosage. Initial lithium dosage is most often calculated via empirical methods and then titrated on the basis of serum lithium determinations to achieve appropriate concentrations.<sup>4-7</sup> However, this method may yield errors in the initial dosage, with associated increased risk of undertreatment or toxicity and a delay in reaching the desired serum concentrations.<sup>3</sup> To lessen these problems, methods for predicting individual dosage requirements have been developed.<sup>8</sup>

There are several methods to predict serum lithium levels.<sup>9-16</sup> Pepin et al<sup>14</sup> developed a method that predicts dosage on the basis of an estimate of the lithium body clearance. This approach does not rely on measuring serum lithium concentrations to make a prediction. According to Patrias and Moore,<sup>10</sup> the Zetin formula overestimates the appropriate dosage of lithium 3 times more frequently than the Pepin formula. Furthermore, the Zetin equation was recently found to be a poor predictor of lithium dose.<sup>17-19</sup>

A more recent study<sup>20</sup> compared the Zetin, Jermain<sup>21</sup> and Pepin a priori methods and an empirical method to predict lithium dosage requirements. The records of 47 patients were used in the study, and dosage and serum concentration data were analyzed to assess the precision and bias of each a priori method. The Jermain and empirical methods significantly overpredicted concentration and underpredicted dosage; the Zetin method overpredicted dosage; and the Pepin method underpredicted dosage but not concentration. The average difference in dosage error among the methods

was 73.3 mg/day. The authors concluded that the 3 methods were similar to an empirical method in their ability to predict lithium dosages.

One of the shortcomings of many previous studies investigating dosage and serum levels of lithium is the retrospective approach taken. To date, only 2 such studies have been conducted prospectively with patients with bipolar disorder.<sup>22,23</sup> Moreover, Rosenberg et al<sup>24</sup> found that a mathematical model used for dose prediction was moderately accurate but tended to predict a lower dose than was actually required, and Markoff and King<sup>25</sup> reported that dose-prediction errors with the Zetin algorithm led to underdosing. Browne et al<sup>26</sup> compared pharmacokinetic and empirical dosing methods and failed to demonstrate any statistically significant differences among the procedures. In light of the above-mentioned difficulties,<sup>27-35</sup> a prospective study is needed to examine the prediction errors of the Pepin method.

## Methods

Participants were recruited through advertisements in local papers. Individuals were eligible to take part in the study if they met the following criteria: 18–50 years of age; no heart, thyroid or kidney conditions; no mental illness; and no general anesthesia in the past 6 months. In addition, women of childbearing age had to be using a reliable method of birth control and have had a negative pregnancy test before inclusion in the trial. All subjects gave full informed consent and were seen in an outpatient setting; compliance rates were monitored as closely as possible.<sup>36-39</sup>

The final sample comprised 15 of 30 healthy volunteers selected for a double-blind, placebo-controlled study of the effects of lithium on cognition.<sup>40</sup>

### *Lithium*

The active agent used in this experiment was a slow-release lithium carbonate (Lithizine) in 150-mg and 300-mg capsules. The initial daily dose was calculated according to the Pepin formula to obtain a desired blood serum lithium level of 0.8 mmol/L, the mean

clinical concentration used in lithium therapy. Blood samples were drawn weekly, in the morning, 12 hours after the last intake of lithium or placebo.

The Pepin formula is written as follows:

$$D = \frac{(C_{ss\_min})(V_{app})(1 - e^{-kt})}{(F e^{-kt})}$$

where D = dosage of lithium in mmol (300 mg lithium carbonate = 8.12 mmol),  $C_{ss\_min}$  = 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 the Pepin equation include:

- To determine ideal weight (kg):  
for men, weight = 50 + 90.551 (height - 1.524)  
for women, weight = 45.5 + 90.551 (height - 1.524)
- To determine clearance of creatinine (mL/min):  
for men,  $Cl_{Cr} = [(140 - \text{age})(\text{weight})]/(72 Cr_S)$   
for women,  $Cl_{Cr} = [0.85(140 - \text{age})(\text{weight})]/(72 Cr_S)$
- To determine clearance of lithium (mL/min):  
 $Cl_{Li} = 0.235(Cl_{Cr})$
- To determine  $t_{1/2}$  (h):  
 $t_{1/2, Li} = t_{1/2, n} / \{1 - Fe [1 - (Cl_{Cr}/100)]\}$ ,  
where  $t_{1/2, n} = 24$  h and  $Fe = 0.95$  (dose excretion).

Daily maintenance dose was adjusted in increments of 300 mg during the treatment phase if the serum lithium concentration was more than 0.2 mmol/L from the target level (i.e., 0.8 mmol/L) or reduced if major side effects were reported.

### Data analysis

The variation between subjects and between weeks was calculated with an analysis of variance; the critical level of significance was set at 0.05.

## Results

Lithium serum concentrations of 15 of 30 healthy volunteers selected for a double-blind, placebo-controlled study of the effects of lithium on cognition<sup>40</sup> were monitored over the study period. One volunteer dropped out during the course of the study and another was removed for medical reasons. The final sample therefore comprised 13 healthy volunteers — 6 women and 7

men (mean age 32 years [range 18–44 years]) with a mean education level of 16 years (range 12–25 years).

Initial daily doses calculated with the Pepin formula ranged from 1050 mg to 1950 mg (mean 1569 mg, standard deviation [SD] 291 mg). Mean lithium serum levels were 0.74 mmol/L (SD 0.19 mmol/L) for week 1, 0.67 mmol/L (SD 0.22 mmol/L) for week 2 and 0.69 mmol/L (SD 0.13 mmol/L) for week 3 (Table 1).

During the first few days of lithium intake, side effects (i.e., headaches, nausea and, less frequently, vomiting and diarrhea) were reported by 4 subjects. In contrast to studies where lithium dosage is increased slowly, 41.7% of the subjects guessed they were receiving lithium. This is likely related to our dosage regimen, where maximum doses were administered at the start to obtain the target serum lithium concentration of 0.8 mmol/L (Fig. 1).

The variation between subjects was greater than that within subjects over time. In fact, the difference between weeks was not significant. To assess the proportion of subjects falling outside the “optimal” therapeutic concentration range, the between-subject variance (i.e., 0.018) was used. Sixty-eight percent of the serum sample concentrations were between 0.57 mmol/L and 0.83 mmol/L, and 84% were in the therapeutic range between 0.6 mmol/L and 1.2 mmol/L.

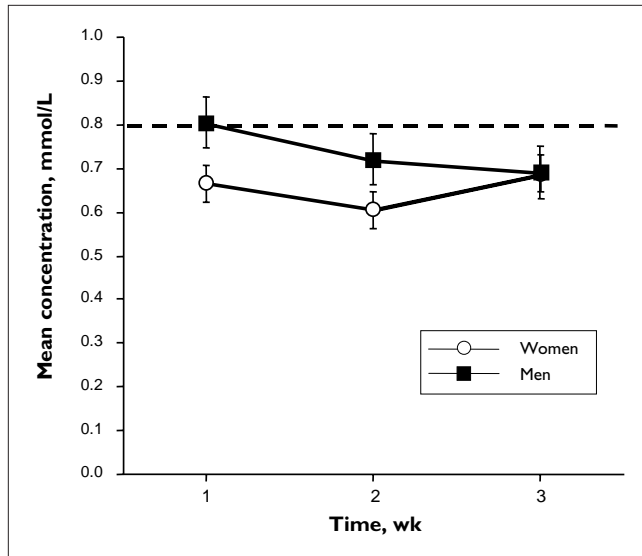
Because the Pepin method was used to achieve a steady-state concentration of 0.8 mmol/L, its predictive performance was estimated by the absolute differences from the 0.8 mmol/L. We first tested, using a general linear model, in function of time, whether the mean of the differences was null. There was no significant statistical difference between times. However, the overall mean serum lithium level of 0.70 mmol/L was significantly different from 0.8 mmol/L ( $F = 5.7, p = 0.034$ ).

Because the actually administered dosage did not correspond to the Pepin dosage, we considered the relative error between the observed lithium concentration and the expected concentrations according to Pepin formula. Once again, there was no significant statistical trend over time. The difference between the overall mean concentration of lithium (0.70 mmol/L, SD 0.15 mmol/L) and the mean of expected concentrations (0.79 mmol/L, SD 0.05 mmol/L) approached significance ( $F = 4.34, p = 0.05$ ). We also examined the difference between the dosage administered and the Pepin dosage needed to reach the concentrations observed. Once again, there was no significant statistical effect of time, but the difference between the mean actual dosage and the mean Pepin dosage required to

obtain the observed concentrations was significant ( $F = 8.28, p = 0.014$ ).

### Discussion

The Pepin method gave reasonable estimates of the



**Fig 1:** Mean serum concentrations of lithium in men ( $n = 7$ ) and women ( $n = 6$ ) participating in the study over a 3-week period.

required dosages to obtain serum lithium levels within the range of 0.6 mmol/L to 1.2 mmol/L for 84% of the samples taken in the study. However, the concentrations of lithium reached were statistically lower than those expected from the Pepin formula. It would appear that the dosages from Pepin formula are conservative. This study confirms Wright and Crismon's<sup>20</sup> report that the Pepin method underpredicts dosage.

Potential limitations to the generalization of our results must be considered. The number of subjects in this study was small and the age range was narrow. In addition, these healthy volunteers were likely to be more treatment compliant than patients with psychiatric disorders. If patients had been included in the investigation, we would have been able to assess the effects of non-adherence.

Because our study was conducted in an outpatient setting, potential biases such as sodium intake and concurrent treatment could not be assessed, particularly with respect to the use of nonsteroidal anti-inflammatory drugs and alcohol. Although subjects were asked to report any changes in their habits, including alcohol and drug use, a lack of such reports should not be interpreted to mean abstinence.

One would also predict that healthy young volunteers would be less likely to be outliers (i.e., require

**Table 1:** Subject characteristics, calculated Pepin dosage\* and serum lithium concentration for 13 healthy volunteers over the 3-week study period

Patient no.	Sex	Height, m	Ideal weight, kg	Age, yr	Creatinine clearance, mL/min	Lithium clearance mL/min	Calculated Pepin dose* mg/day	Actual dose, mg/day	Week; serum lithium concentration, mmol/L		
									1	2	3
1	M	1.76	71.37	31	0.87	29.18	1960	1950	0.80	0.90	0.80
2	M	1.78	73.18	43	0.87	26.63	1718	1650	0.70	0.80	0.90
3	M	1.75	70.46	18	0.99	28.34	1878	1950	1.10	1.20	0.90
4	M	1.75	70.46	38	0.95	24.69	1545	1500	0.70	0.40	0.50
5	M	1.69	65.03	23	0.88	28.22	1867	1800	1.10	0.60	0.55
6	M	1.73	68.65	31	0.89	27.44	1793	1800	0.49	0.43	0.54
7	M	1.72	67.75	34	1.03	22.76	1381	1350	0.74	0.71	0.64
8	F	1.70	61.44	29	0.87	21.75	1299	1350	0.70	0.80	0.60
9	F	1.74	65.06	20	0.79	27.42	1790	1800	0.50	0.42	0.65
10	F	1.60	52.38	44	0.74	18.85	1077	1050	0.77	0.66	0.77
11	F	1.57	49.67	34	0.66	22.13	1330	1350	0.51	0.59	0.76
12	F	1.70	61.44	36	0.70	25.32	1600	1650	0.81	0.55	0.75
13	F	1.64	56.00	43	0.77	19.57	1131	1200	0.70	0.61	0.60
Mean		1.70	64.07	33	0.85	24.79	1567	1569	0.74	0.67	0.69
SD		0.06	7.51	9	0.11	3.47	297	291	0.19	0.22	0.13

Note: M = male, F = female, SD = standard deviation.

\*Calculated to obtain a therapeutic lithium serum concentration of 0.8 mmol/L at steady state.

dosages much higher or lower than the mean); but this is where the real clinical value of prediction techniques lies.

Our study was not designed to provide data that we could compare with results obtained using other mathematical methods to predict initial lithium dosage. Therapeutic monitoring of lithium is highly amenable to a mathematical approach because of the lack of metabolic confounds. Moreover, Sproule et al<sup>42</sup> report that "fuzzy logic" can be used for pharmacokinetic modeling for predicting serum lithium concentrations.<sup>42</sup>

Prediction of the daily dose of lithium necessary to achieve concentrations within the therapeutic range is highly relevant to clinical practice, and our results indicate that Pepin method is probably a safe method to predict the appropriate daily dose of lithium.

## Conclusion

An accurate, unbiased and safe method for predicting appropriate lithium dosage would be an asset to clinical practice. There have been a number of methods proposed in the literature, but none are used in routine clinical practice. Although our data support the use of the Pepin method, the method relies heavily on the calculated creatinine clearance for parameter estimations. It is therefore not surprising that a small group of young healthy subjects with normal renal function would perform similarly with this prediction method. What is needed in the future is an evaluation of this method in a wide range of patients with varying degrees of renal dysfunction.

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**Competing interests:** None declared.

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