Lithium dose prediction based on 24 hours single dose levels: a prospective evaluation

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Abstract
The authors present the results of the utilization of a pharmacokinetic prediction test for lithium posology. Based on a single point (plasma lithium determination 24 h after a single dose) such a test aims to adapt the posology as soon as the second day of treatment rather than after one week as clinicians must wait for a steady state to be achieved.

Built on the previous work of Perry, the test targeted the plasma lithium level at 0.8 ± 0.1 mmol l⁻¹.

Thirty-one patients took part in the study. There were two drop-out cases and the results were available for 29 patients: among them, 51% had their plasma level in the targeted zone. Although there was no control group, the prediction test often allowed us to use a higher dose than the usual fixed dose whose amount is limited by the risk of overdosing for the slower metabolizers.

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1. Introduction
Since the work of Cade in 1949 [1] and Schou [2], a great deal of research has proved the efficacy of lithium salts in the treatment of bipolar disorders [3,4]. Nowadays, in the field of affective disorders, it is recognized as a treatment for acute mania, long term prophylaxis of bipolar disorders, acute treatment of depression especially in bipolar disorders and augmentation of antidepressant response. From the very beginning, its use was limited by the narrow therapeutic index and the risk of severe side effects and toxicity when lithium plasma level is above 1.5 mmol l⁻¹ [5]. It is widely recognized that there is a strong correlation between plasma concentration and efficacy. The recommended lithium plasma level ranges for treatment of acute mania and for prophylaxis of bipolar and unipolar disorders, are respectively 0.8–1.2 mmol l⁻¹ and 0.6–0.8 mmol l⁻¹ [6].

Regarding lithium kinetics, we know that lithium is distributed unevenly into different body compartments. It is not metabolized and is eliminated primarily through the kidneys. The elimination correlates with the renal function. A decrease clearance can be observed in different situations such as old age, dehydration, chronic administration of different medication (diuretics, NSAIA) and chronic lithium administration [7].

As economic pressures work toward reducing the length of psychiatric hospitalizations, it is vital to develop more rapid methods of controlling acute and severe psychiatric symptoms. It is also in the patient’s best interest to achieve alleviation of severe psychiatric symptoms as rapidly as possible. Towards this end, efforts have been made to predict, at a steady state, what dose of lithium salts will result in a therapeutic plasma level in a given patient.

Cooper et al. [8] pioneered those efforts by observing a strong linear correlation between the lithium plasma level 24 h after a loading dose (600 mg of lithium carbonate) and the lithium plasma level at steady state. On the basis of this determination, they calculated the daily dose required to maintain a lithium plasma concentration of 0.6–1.2 mmol l⁻¹. Two studies confirmed the validity and the reproducibility of this predictive method [9,10].

In the 1980s, Zetin et al. [11,12] proposed a statistical approach. They established an equation calculating a lithium dose corresponding to the desired lithium plasma level using different patients’ variables. Reproducible studies failed to confirm the accuracy of this statistical method. The major problem was the lack, in this equation, of a variable taking into account the renal function [13–15].
At the same time, Perry tried to improve Cooper’s approach [16]. He proposed two methods of calculating the lithium’s posology:

1. The multiple points method: the lithium serum level is measured at 12 and 36 h after a loading-dose of 1200 mg lithium carbonate.
2. The single point method: the lithium serum level is measured at 24 h after a loading-dose of 1200 mg lithium carbonate.

He studied the validity of his prediction table on 38 patients. Two subgroups were constructed depending on the therapeutic goal: prophylaxis or treatment of acute mania. For both, he chose a broad target zone 0.41–0.89 and 0.9–1.3 mmol l$^{-1}$, respectively. Eighty-three percent of the patients in the first group were in the target zone as well as 80% of the second group.

In 1988, Browne published a retrospective study [17] on different pharmacokinetic methods including those of Perry, Cooper and Zetin. Data analysis was based on evaluation of prediction error or the difference between the predicted steady-state lithium concentration and the measured steady-state concentration at equivalent daily doses. Each dosing method was assessed with regard to accuracy and bias of predicted steady-state serum lithium concentration. From a statistical point of view, combining precision and concentration deviation of the results, Perry’s single point method seemed to be the most accurate. For patients with renal insufficiency, the multiple points method was recommended.

Taking into account these different points of view, we constructed a lithium prediction table based on Perry’s single point method. It was important for us to adapt Perry’s model to the Swiss clinical setting and in particular to the lithium preparation at our disposal on our market. We studied prospectively, the validity of such a predictive table. The goal was to construct a handy tool enabling the accurate attainment of a lithium steady state.

2. Method

2.1. Construction of the prediction table

Bearing in mind the linear ratio between dose and concentration, we can establish the following equation:

$$D = \frac{target
dose}{administered
dose} \times \frac{target\nconcentration}{predicted\nconcentration}$$

• Target dose ($D$): The dose, we want to determine with the prediction test, is expressed as tablets of Lithiofor® (see fixed dose).
• Target concentration: The plasma level we wish to reach at steady state with the help of the prediction test. Based on literature consensus, we have fixed it at 0.8 mmol l$^{-1}$ (considering the interval 0.7–0.9 mmol l$^{-1}$ as acceptable).

### Table 1

<table>
<thead>
<tr>
<th>Lithium serum level at 24h ($C_{24h}$) (mmol l$^{-1}$)</th>
<th>Lithiofor® daily dose (tablet per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;0.25$</td>
<td>3.5</td>
</tr>
<tr>
<td>0.26–0.31</td>
<td>3</td>
</tr>
<tr>
<td>0.32–0.39</td>
<td>2.5</td>
</tr>
<tr>
<td>0.40–0.52</td>
<td>2</td>
</tr>
<tr>
<td>0.53–0.76</td>
<td>1.5</td>
</tr>
<tr>
<td>0.77–1.37</td>
<td>1</td>
</tr>
<tr>
<td>$&gt;1.37$</td>
<td>0.5</td>
</tr>
</tbody>
</table>

• Administered dose: Indicated by Perry’s protocol: 1800 mg lithium carbonate containing 48.8 mmol lithium. For institutional reasons, we had to use lithium sulfate (Lithiofor®). A lithium sulfate tablet contains 12 mmol of lithium. Thus, the approximate equivalent of 1800 mg lithium carbonate expressed in tablets is 4.

• Predicted concentration: The hypothetical concentration, we would obtain at steady state using the administered dose, knowing the plasma concentration 24 h after the dose test ($C_{24h}$). Perry’s equation [16] allows us to calculate this predicted concentration ($C$) = 0.131 + 3.29 × $C_{24h}$ (concentration obtained 24 h after the loading dose).

From the initial equation:

$$D = \frac{target\nconcentration \times \text{administered\ndose}}{predicted\nconcentration}$$

We obtained:

$$D = \frac{0.8 \text{ mmol l}^{-1} \times 4}{0.131 + 3.29 \times C_{24h}} = \frac{3.2}{0.131 + 3.29 \times C_{24h}}$$

Lithiofor® is at disposal in tablets which can be divided. Thus, using this last equation, we constructed a prediction table (see Table 1) which indicates for a certain value of $C_{24h}$ the number of tablets of Lithiofor® to target the steady-state plasma level of 0.8 mmol l$^{-1}$.

Concerning the test dose, Perry proposed 1200 mg lithium carbonate (32.4 mmol Li). In Switzerland, as we do not have any lithium carbonate with normal release, we used lithium acetate: Quinolorm®. The acceptable equivalent is four tablets Quinolorm®: i.e. 2144 mg lithium acetate (1 tablet: 8.0 mmol l$^{-1}$).

2.2. Practical use of the prediction test

- At day 0, at 8:00 a.m., the patient took four tablets Quinolorm®.
- At day 1, exactly at 8:00 a.m., a blood sample to test lithium plasma level was drawn. The patient then received one tablet of Lithiofor® (lithium sulfate). In the afternoon, as the physician received the lithium plasma level, he could determine with the prediction table how many Lithiofor® tablets (taking into account the tablet received in the morning) the patient needed to receive.
- At day 2 and after: the patient received the number of tablets determined by the prediction table: half in the morning and half in the evening (when it was not possible to have two identical halves, the higher dose was given in the evening).
- At day 6 (steady state), a lithium plasma level control was done.

3. Ethics

The use of the prediction test was initially part of another study on depression treatment. This study was approved by the Ethical Committee of our Department. Patients received information, including about the prediction test and gave their written consent. With the unfolding of the study and the good results concerning the fidelity of the prediction test, we used it as a routine technique for a few patients, not included in the depression treatment study. However, according to the regulatory rules of our department concerning any pharmacological treatment, they were informed and gave their oral consent.

4. Results

4.1. Study population

In this open study conducted at the Adult Psychiatric Clinic of Geneva, we included 33 patients (29 inpatients, 4 outpatients). Two patients (both outpatients) dropped out because of gastrointestinal side effects (vomiting in the hours...
following the administration of Quinolorm™). They were excluded from the study and were not included in the final results analysis. The final repartition (n = 31) was 12 men for 19 women. Average age was 44 (± 9 years).

No patient had any renal dysfunction and plasmatic creatinine was in a normal range (0.9 ± 1.4 mmol l⁻¹) for all the patients.

According to the international classification ICD-10 [18], 96.8% suffered from affective disorders (35.5% bipolar disorders (F 31) and 3.3% depressive disorders (F 32 and F 33)). One patient suffered from schizoaffective disorder (F 25).

After the prediction test, they received on average 2.1 ± 0.5 tablets per day Lithiofor® (range: 1.5–3). Co-medication was allowed and unrestrictive.

4.2. Prediction test results

Among the 31 remaining patients, 16 (51.6%) had a lithium plasma level on day 6 of between 0.7–0.9 mmol l⁻¹, i.e. in the target zone. Seven (22.6%) had a lithium plasma level < 0.7 mmol l⁻¹. Eight (25.8%) had a plasma lithium level > 0.9 mmol l⁻¹. Among these, one patient had a lithium plasma level in the toxic area (1.3 mmol l⁻¹) but it was clinically well tolerated by the patient.

Fig. 1 presents the distribution at day 6 of lithium plasma levels.

5. Discussion

The results confirm the interest of using a prediction test to initiate lithium treatment even if it remains clear that with lithium treatment, long term therapeutic drug monitoring is still required. With a target lithium plasma level of 0.8 mmol l⁻¹ (±0.1 mmol l⁻¹), 51.6% of the patients are within the range at steady state at day 6. One patient with lithium plasma level at 1.32 mmol l⁻¹ was within a potentially toxic range but without any clinical signs of toxicity. It is important to note that this patient received after the prediction test the dose of 1.5 Lithiofor® tablet per day which is the usual dose in clinical practice in our unit (see below).

At day 6, we found no significant correlation between sex, weight, age, plasma urea, plasma creatinine on one hand and steady-state lithium plasma level on the other hand.

If we compare our results with the literature, we see that 80% of Cooper’s patients (n = 17) were in the target zone but this zone was very broad (0.6–1.2 mmol l⁻¹). If we had chosen such a broad target zone, i.e. 0.5–1.1 mmol l⁻¹, 93.6% of our patients would have been in the range. As quoted before, Perry studied the validity of his prediction table on 38 patients. He constructed two subgroups depending on the therapeutic goal: prophylaxis or treatment of acute mania. For both, he chose a broad target zone: 0.41–0.89 mmol l⁻¹ and 0.9–1.3 mmol l⁻¹, respectively. Eighty-three percent of the patients of the first group were in the target zone and for the second group, 80%.

Here also the target zone was broader than the one we chose. With Perry’s study, 80% of the patients were in the 0.9–1.3 mmol l⁻¹ target zone; for our study, 70% were in the 0.6–1.0 mmol l⁻¹ range.

For all the subjects, renal function was conserved. They were all lithium naive subjects. Thus, lithium clearance is likely to be rapid. We can suggest, knowing lithium kinetics, that the prediction test should be used with great precaution in situations where the renal clearance is impaired (old age, lithium chronic administration for example).

To evaluate the usefulness of the prediction test, it would have been necessary to include a control group as this would have allowed comparison on different outcome measures: not only steady-state plasma level but also time to remission or duration of hospital stay. It was the main limitation of our study. To partially compensate for it however it is possible to consider for our group of patients the results we would have obtained using different fixed doses and to determine how many would be below, in, or above the target plasma level interval. For this purpose we again used the proportionality between dose and plasma level:

dose suggested by prediction test = administered dose × concentration obtained with the prediction test / theoretical concentration obtained with the administered dose

One of the dangers of this empirical method is to risk more patients within the toxic range.

With Lithiofor® 1.5 tablets per day, the usual initial dose in our department before the use of the prediction test, the same patient would have reached the same potentially toxic plasma level of 1.32 mmol l⁻¹ as with the prediction test. With Lithiofor® 2 tablets per day this patient would have reached a clearly dangerous plasma level (1.7 mmol l⁻¹).

Table 2

| Theoretical lithium plasma level with two different fixed dose and real lithium plasma level with the prediction test (n = 31) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | ≤0.7 mmol l⁻¹    | 0.7–0.9 mmol l⁻¹ | >0.9 mmol l⁻¹   | >1.5 mmol l⁻¹   |
| Lithiofor® 1.5 tablets per day  | 27 (87.1%)       | 3 (3.22%)       | 3 (9.68%)       | 0%              |
| Lithiofor® 2 tablets per day   | 18 (58%)         | 9 (29%)         | 3 (9.68%)       | 1 (3.22%)       |
| Lithiofor® with the prediction test | 7 (22.6%)   | 16 (51.6%)      | 4 (25.8%)       | 0%              |
The other problem of the administered dose is the high proportion of low plasma levels. Table 2 shows clearly that with the usual administered dose, most of the patients have non-therapeutical lithium plasma level and that if the fixed dose is increased, the toxicity danger is beyond what can be accepted.

Several other limitations should be noted when interpreting the results of the present study. First of all, the sample is small ($n = 31$). Second, for institutional reasons, we had to use two different lithium salts. In Perry’s single method, which inspired our prediction table, he used a single salt: lithium carbonate.

Another point which needs further investigation is that two patients vomited after the initial lithium dose. They represent half of the outpatients ($n = 4$). None of the inpatients exhibited such problems of intolerance.

Even if there was no correlation between any patient variable and lithium steady-state plasma level, we wished to examine whether the performance of the prediction test given by the lithium plasma level at steady state was equivalent for slow and rapid lithium metabolizers (indicated by the lithium plasma level at day 1). As we can see in Fig. 2, there is a tendency for both the rapid and the slow metabolizers to have, at steady state, higher lithium plasma level than intermediate metabolizers. We propose thus to modify the prediction table (see Table 3). Doing so, we would perhaps limit the risk of excessive dosing (the patient with the pretoxic lithium plasma level at steady state was the patient with the highest 24 h plasma level).

In future, this new prediction table should be tested in a prospective way and on a larger sample. Our results suggest that this simple procedure may help the clinician to better adjust lithium treatment very early.

### Table 3

<table>
<thead>
<tr>
<th>Lithium plasma level at day 1 (mmol l$^{-1}$)</th>
<th>Lithiofor® (tablet per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 0.39$</td>
<td>2.5</td>
</tr>
<tr>
<td>$0.40 - 0.52$</td>
<td>2</td>
</tr>
<tr>
<td>$0.53 - 0.60$</td>
<td>1.5</td>
</tr>
<tr>
<td>$\geq 0.61$</td>
<td>1</td>
</tr>
</tbody>
</table>

References