Use of fractional lithium clearance in clinical and epidemiological investigation: a methodological assessment

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SUMMARY

1. The fractional clearance of lithium (FC Li) has been validated in the rat under controlled experimental conditions as a reliable indicator of sodium and water handling in the proximal tubule. The purpose of the present study was to evaluate some key methodological aspects related to the use of the FC Li in clinical and epidemiological investigation.

2. FC Li was determined in healthy normotensive, or in some cases, in borderline/mild essential hypertensive subjects, by a morning urine collection obtained between 09.00 and 13.00 hours after a 300 mg oral lithium carbonate load (= 8.1 mmol of elemental lithium).

3. The ratio of intra-individual to inter-individual variance of FC Li, measured in free-living subjects on unrestricted diet, was shown to be low enough (0.33) to allow adequate characterization of individuals in a population with a single measurement, or at most with two (compared with at least four measurements needed to characterize the fractional excretion of sodium).

4. The remarkable influence of dietary sodium intake on FC Li, demonstrated under metabolic ward conditions, might explain a major portion of the observed intra-individual variability.

5. At the dosage employed in the present study, oral lithium administration did not affect the renal handling of sodium, potassium or calcium. Likewise, it did not induce any change in a series of 17 metabolic parameters and indicators of renal and liver function.

6. It is concluded that the FC Li may be a safe and useful tool for the clinical and epidemiological investigation of renal sodium and water handling. The possibility of a confounding effect of dietary sodium intake, however, should be kept in mind.

Key words: hypertension, inter-individual variability, intra-individual variability, lithium clearance, sodium intake.

Abbreviations: FC Li, fractional clearance of lithium; FC Na, fractional clearance of sodium.

INTRODUCTION

A recent report on abnormalities of sodium handling in the proximal tubule of patients with essential hypertension [1] was based upon the measurement of the renal clearance of lithium after oral administration of a lithium load. The ratio of lithium clearance to glomerular filtration rate, later referred to here as fractional clearance of lithium (FC Li), is assumed to provide a close estimate of the sodium and fluid delivery from the proximal tubule to the loop of Henle, in as much as the lithium ion is re-absorbed in parallel with sodium in the proximal tubule and, in normal physiological conditions, it is neither re-absorbed nor secreted in further segments of the nephron [2–6]. Recently, this index of proximal tubular sodium handling has been effectively validated against conventional micropuncture techniques in the anaesthetized Sprague–Dawley rat [7]. On the other hand, some limitations to the use of the lithium clearance method ought to be kept in mind, i.e. during severe sodium restriction where some lithium reabsorption certainly occurs at distal tubular sites [8] or during osmotic diuresis, due to presence in the tubular fluid of non-reabsorbable, or only partially reabsorbable, solutes (mannitol, glucose, urea) which may introduce a serious bias in the estimate of proximal tubular fluid and sodium delivery to Henle's loop [9].

The use of lithium clearance in clinical investigations has the advantages of being relatively simple, inexpensive, safe and fully acceptable to human subjects and patients; it is, however, difficult to evaluate the strength of clinical
and epidemiological observations of proximal tubular sodium handling based on the measurement of lithium clearance in free-living individuals before an assessment is made of some methodological aspects, which have either not been systematically investigated so far in man, or are still a matter of controversy.

The following questions, in particular, were identified as crucial and were addressed in the present study. (1) What is the intra- and the inter-individual variability of $FCLi$ in man, in free-living conditions? (2) To what extent do changes in dietary sodium intake influence $FCLi$? (3) Does lithium, at the dosage employed for determination of $FCLi$, interfere with the renal handling of other electrolytes, in particular the sodium, potassium and calcium ions? (4) Does lithium administration have any effect on the main indices of renal and liver function and on various metabolic parameters?

METHODS

All subjects were clinically healthy men or women, free of major disease; they volunteered to participate after having received complete information about the aims of the study and the procedures to be employed.

In all the studies $FCLi$ was determined as follows. At 22.00 hours, 3 h after the evening meal, a 300 mg lithium carbonate capsule, delivering 8.1 mmol of elemental lithium, was taken by the subject. From 07.00 to 11.00 hours the next morning a 4 h urine collection was obtained and, at the mid-point of the collection, a 5-10 ml sample of venous blood was drawn into a Vacutainer tube. The subject was required to remain fasting overnight and until completion of the study. He/she was invited to drink 200 ml of tap water on taking the lithium carbonate capsule and, again, at the beginning and at the mid-point of the urine collection, in order to maintain an adequate urine flow. Patients were ambulant during the clearance studies, but they were requested to remain in the hospital area and not to engage in any physical activity.

Creatinine, lithium, sodium and, in some experiments, potassium and calcium concentrations were determined in portions of the urine and serum samples. Creatinine was measured by the picric acid colorimetric method; serum and urinary lithium as well as urinary calcium were measured by atomic absorption spectrophotometry with a Perkin-Elmer model 300 spectrophotometer; serum and urinary sodium and potassium as well as serum ionized calcium were measured by ion-selective electrodes, using respectively a Beckman Electrolyte EA2 and an Orion SS-20 analyser.

Throughout this paper the lithium, sodium, potassium and calcium clearances are expressed as fractional clearance, i.e. as the ratio of the clearance of the given substance to the clearance of creatinine (used as an estimate of the glomerular filtration rate). In preliminary tests performed in four subjects, the plasma lithium kinetics were determined under the experimental conditions described above by obtaining a 2 ml blood sample every hour between 07.00 hours and 15.00 hours; the results of these tests showed a very good linear correlation ($r = -0.99$) of the logarithmic serum lithium concentration with time during this interval (Fig. 1).

Study 1

In order to assess the intra- and inter-individual variability of $FCLi$ (and fractional clearance of sodium, $FCNa$) in free-living conditions, these were determined three times at 2 week intervals in 11 healthy volunteers (nine male, two female), aged 25–58 years [mean 33.8 ± SEM 2.9 years]. $FCLi$ and $FCNa$ were measured while the subjects were on their customary diets and were allowed to perform their habitual daily activities, with avoidance of vigorous exercise.

The differences in the mean values of the triplicate set of measurements of $FCLi$ and $FCNa$ were tested by one-way analysis of variance with repeated measures, according to standard statistical methods [10], with the aid of a Hewlett-Packard 85 computer system.

The overall intra-individual SD for both $FCLi$ and $FCNa$ (a measure of their intra-individual variability), was estimated, according to Liu et al. [11], from the respective triplicate values of the 11 subjects, as:

$$
\delta_e = \left[ \frac{\sum_{j=1}^{J} \sum_{i=1}^{I} (x_{ij} - \bar{x}_i)^2}{J(J-1)} \right]^{1/2}
$$

where $x_{ij}$ is the value for the $j$th measurement in the $i$th individual and

$$
\bar{x}_i = \frac{\sum_{j=1}^{J} x_{ij}}{J}
$$

is the mean of the $j$ replicates on the $i$th individual, $I$ is the sample size and $J$ is the number of replicate measurements made on the same individual. This formula is a general expression of the technical error formula which applies to the situation where only two replicates are taken and $d$ represents the difference between them:

$$
\left( \frac{\Sigma d^2}{2N} \right)^{1/2}
$$

The intra-subject variability determined in such a way in fact includes both the biological variability and the
technical error; the latter, however, is very small given the excellent repeatability of the creatinine as well as of the electrolyte determinations in biological fluids. The squared intra-individual \( \sigma^2 \) will provide the intra-individual variance.

The inter-individual variance \([11]\) was estimated by:

\[
\sigma^2_I = \sigma^2 \left( \frac{\rho}{1-\rho} \right)
\]

(2)

where \( \sigma^2_I \) is the intra-individual variance previously calculated for the same population and \( \rho \) is the average of the estimated correlation coefficients between all \( FC_{Li} \) (or \( FC_{Na} \)) measurements. The square-root of the inter-individual variance is the inter-individual \( sd \).

With respect to the analysis of statistical associations of \( FC_{Li} \) (or \( FC_{Na} \)) with another given variable, the following formula \([11]\) allows us to estimate the percentage diminution of the correlation coefficient between \( FC_{Li} \) (or \( FC_{Na} \)) and the second variable of interest, due to the intra-individual variability of \( FC_{Li} \) (or \( FC_{Na} \)).

\[
\left( 1 - \frac{1}{\sqrt{1+ (\sigma^2_I/\sigma^2)} \times 100}
\]

(3)

where \( \sigma^2 \) is the intra-individual variance of \( FC_{Li} \) (or \( FC_{Na} \), \( \sigma^2_I \) is the inter-individual variance of \( FC_{Li} \) (or \( FC_{Na} \)) and \( J \) is the number of measurements made. The assumption is made in these calculations that the second variable in the correlation has an intra-individual variability of zero.

Conversely, the number of measurements of \( FC_{Li} \) (or \( FC_{Na} \)) required to limit the diminution of the true correlation coefficient to less than \( 100 \times (1-p) \% \) could be estimated by \([11]\):

\[
J = \left( \frac{p^2}{1-p} \right) \times \frac{\sigma^2}{\sigma^2_I}
\]

(4)

where \( p \) is a number satisfying the condition \( 0 < p < 1 \).

**Study 2**

To investigate the effect of changing dietary sodium intake on \( FC_{Li} \), eight subjects (three male, five female) aged 42.4 (SEM 3.6) years, with borderline or mild essential hypertension (diastolic blood pressure between 90 and 104 mmHg on at least two clinic visits), free of target organ disease and not on medical treatment, were studied in the metabolic ward over three consecutive 1 week periods. At entry into the study, the subjects were placed on a standard 40 mmol sodium diet, to which a different number of sodium chloride (Slow Na, Ciba) or identical placebo tablets were added in order to achieve three different levels of sodium intake: 125, 40 and 210 mmol/day. Twenty-four hour urinary sodium excretion was measured on the last 3 days of each period and the mean of the three values was taken as an index of the actual sodium intake of the patient in each period. \( FC_{Li} \) and \( FC_{Na} \) were determined on the last day of each period by the procedure described above.

**Study 3**

An evaluation of the effects of lithium carbonate on the renal sodium and potassium handling was carried out in 21 subjects (eight males, 13 females), aged 47.9 (SEM 2.7) years with borderline or mild essential hypertension, free of target organ disease and not on pharmacological treatment. These subjects were admitted to the metabolic ward and placed for 7 days on a fixed sodium diet. \( FC_{Na} \) and the fractional clearance of potassium were determined on urine collections obtained between 07.00 and 11.00 hours on the last 2 days of diet, the first measurement serving as the control value, the second one after the administration of a 300 mg lithium carbonate capsule at 22.00 hours. In nine out of 21 patients (three males, six females), the fractional clearance of calcium was also measured on the same occasions. Statistical evaluation of the data was by Student’s \( t \)-test for paired observations.

**Study 4**

The possible effects of lithium administration on plasma sodium, potassium, calcium, phosphate, urea, glucose, creatinine, total protein, albumin, uric acid, bilirubin, cholesterol, triglyceride, aspartic and alanine aminotransferase, alkaline phosphatase and \( \gamma \)-glutamyltransferase were investigated in 12 volunteers (six males, six females) aged 51.2 (SEM 2.5) years, by measuring these parameters on a fasting venous blood sample collected in the morning between 08.00 and 10.00 hours on 2 consecutive days, the first measurement serving as the control value, the second one after the administration of oral lithium carbonate (300 mg) at 22.00 hours.

**RESULTS**

**Intra- and inter-individual variability of \( FC_{Li} \)**

Fig. 2 shows the mean and the range of triplicate values obtained in the 11 free-living subjects in whom the \( FC_{Li} \) was measured repeatedly at 2 week intervals. Table 1 gives the mean and the \( sd \) for each set of triplicate determinations, the overall mean and its \( sd \), the estimated overall intra-individual and inter-individual \( sd \) and the ratio of intra-individual to inter-individual variance, for both \( FC_{Li} \) and \( FC_{Na} \).

Mean values of triplicate determinations of either \( FC_{Li} \) or \( FC_{Na} \) were not significantly different when tested by analysis of variance with repeated measures.

The overall intra-individual \( sd \) of \( FC_{Li} \), estimated from the triplicate values of the 11 subjects, was 1.99 in absolute value (8.5% of the overall mean). The intra-individual \( sd \) for \( FC_{Na} \) was 0.27 (22.5% of the overall mean). The intra-individual variances were respectively 3.96 and 0.075.

The inter-individual variances of \( FC_{Li} \) and \( FC_{Na} \) were respectively 11.88 and 0.078; accordingly, the inter-individual \( sd \) were respectively 14.7% and 24.9% of the overall mean.

The ratio of intra-individual to inter-individual variance was 0.33 for \( FC_{Li} \) and three times greater (0.96) for \( FC_{Na} \).
Fig. 2. Fractional clearance of lithium (mean and range of triplicate values) in 11 volunteer subjects (see the text for details).

Table 1. Intra- and inter-individual variability of fractional clearance of lithium and fractional clearance of sodium in a group of 11 healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>FC_{Li}</th>
<th>FC_{Na}</th>
</tr>
</thead>
<tbody>
<tr>
<td>First determination</td>
<td>23.8 (4.8)*</td>
<td>1.12 (0.42)*</td>
</tr>
<tr>
<td>Second determination</td>
<td>22.9 (3.4)*</td>
<td>1.11 (0.38)*</td>
</tr>
<tr>
<td>Third determination</td>
<td>23.7 (3.3)*</td>
<td>1.11 (0.38)*</td>
</tr>
<tr>
<td>Overall</td>
<td>23.4 (3.6)*</td>
<td>1.12 (0.33)*</td>
</tr>
<tr>
<td>Intra-individual SD</td>
<td>1.99 (8.50%)†</td>
<td>0.27 (24.4%)†</td>
</tr>
<tr>
<td>Inter-individual SD</td>
<td>3.45 (14.7%)†</td>
<td>0.28 (24.9%)†</td>
</tr>
<tr>
<td>Ratio (intra-/inter-individual variance)</td>
<td>0.33</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Mean (SD).
†Intra- and inter-individual standard deviations, expressed as percentage of the overall mean, are given in parentheses.

Effect of changing dietary sodium intake on FC_{Li}

In the eight subjects studied in the metabolic ward, mean values of 24 h urinary sodium excretion on the last 3 days of each experimental period were: 117 (SEM 11), 44 (8) and 206 (23) mmol/day, for the intermediate, low and high sodium intake periods, respectively. Changing sodium intake in these patients had an obvious influence on FC_{Li}. Mean FC_{Li} was 26.2 (2.0)% at the end of 7 days on a sodium intake of 125 mmol/day, this value dropped to 21.5 (1.4)% after 7 days on an intake of 40 mmol/day and subsequently rose to 29.4 (1.6)% after 7 days on a sodium intake of 210 mmol/day. This trend was statistically significant ($F=12.3$, $K=3$, and $df=14$, $P<0.001$), as were the differences between mean FC_{Li} on 40 mmol of sodium/day and mean FC_{Li} on either 125 ($P<0.05$) or 210 ($P<0.01$) mmol of sodium/day (using Tukey's test for multiple comparisons).

As shown in Fig. 3, the FC_{Li} fell by at least two percentage points in seven out of eight patients on changing from a sodium intake of 125 mmol/day to one of 40 mmol/day; conversely, it rose by more than five percentage points in six out of eight patients on switching back from 40 to 210 mmol of sodium/day.

Effect of lithium administration on renal electrolyte handling

As shown in Table 2, there was no significant change in the mean FC_{Na} or fractional clearance of potassium after...
the administration of 300 mg of lithium carbonate in the 21 tests performed under metabolic ward conditions on a fixed sodium intake. In the nine cases in which the fractional clearance of calcium was also measured, there was likewise no change in this parameter after lithium administration.

Effect of lithium administration on routine serum biochemistry

Table 3 gives the mean and SEM for the biochemical parameters measured before and after the oral lithium load in 12 volunteers; none of the differences observed was either statistically significant or biologically meaningful.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Li</th>
<th>After Li</th>
<th>d</th>
<th>n</th>
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<tbody>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>145 (1)</td>
<td>144 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ (mmol/l)</td>
<td>4.3 (0.1)</td>
<td>4.4 (0.1)</td>
<td></td>
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<tr>
<td>Total Ca²⁺ (mmol/l)</td>
<td>2.3 (0.02)</td>
<td>2.3 (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.4 (0.06)</td>
<td>1.2 (0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>5.5 (0.7)</td>
<td>6.2 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.8 (0.3)</td>
<td>5.2 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>97 (9)</td>
<td>97 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein (g/l)</td>
<td>70 (2)</td>
<td>67 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42 (2)</td>
<td>40 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid (μmol/l)</td>
<td>333 (30)</td>
<td>327 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>10 (2)</td>
<td>9 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.2 (0.4)</td>
<td>4.9 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.3 (0.1)</td>
<td>1.3 (0.1)</td>
<td></td>
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</tr>
<tr>
<td>Aspartic aminotransferase (μkat/l)</td>
<td>0.3 (0.03)</td>
<td>0.2 (0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (μkat/l)</td>
<td>0.3 (0.08)</td>
<td>0.2 (0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (μkat/l)</td>
<td>2.9 (0.2)</td>
<td>2.8 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-Glutamyltransferase (μkat/l)</td>
<td>0.5 (0.2)</td>
<td>0.4 (0.1)</td>
<td></td>
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</tr>
</tbody>
</table>

DISCUSSION

The aim of the present work was the investigation of some important methodological aspects of the use of FC_Li as an index of proximal tubule fluid and sodium handling.

A very important factor which limits the capability to detect true biological correlations in clinical and epidemiological studies is the ratio of intra-individual to inter-individual variation for the variables that are potentially related. For statistical associations to be detected, the goal of an optimal characterization of the subjects under investigation with respect to the target variables is crucial; this goal will be achieved if each subject in the study population varies from himself over time (intra-individual variability) much less than he varies from the other individuals in the same population (inter-individual variability). If the opposite is true, the objective of adequate individual characterization will not be achieved. A well-known illustration of this problem is given by the putative correlation between blood pressure and 24 h urinary sodium excretion explored in many population studies. It was suggested that one of the reasons for the inability of most such studies to demonstrate this association within a population is the extremely large ratio of intra- to inter-individual variation in individuals with respect to 24 h sodium excretion [13]. In their careful methodological study, Liu et al. [11] showed that, due to this problem, the true correlation coefficient between 24 h sodium excretion and an other given variable, i.e. blood pressure, will be diminished by as much as 52% when only one urine collection is relied upon to characterize individuals, assuming that the intra-individual variation for the other variable under investigation is zero.

Although clinical observations carried out in patients on lithium therapy for manic-depressive disorders seemed to suggest lower within-individual variability for lithium clearance [12], to our knowledge no systematic analysis of this problem has so far been performed. The results of the present study demonstrate that the intra-individual variation of FC_Li, although not negligible, is relatively low: in particular, it is three times lower than that of FC_Na. Accordingly, the ratio of the intra- to the inter-individual variance, the best indicator of the discriminating capacity of the test, appears to be satisfactory (0.33), particularly so when compared with that found for the sodium clearance (0.96) and with that reported by Liu et al. [13] for the 24 h sodium excretion (3.2). Based on the estimated intra- and inter-individual variance of FC_Li by eqn. (3) in the Methods section, it can be shown that the percentage diminution of the correlation coefficient between FC_Li and another potentially related variable, would be 13.3% with a single measurement of the FC_Li. According to eqn. (4), to limit this diminution to less than 15% (a reasonable goal), a single measurement would be satisfactory. At least three measurements would be necessary for FC_Na.

Although these extrapolations ought to be made with some caution in as much as the number of individuals examined was not very large, it appears that the variation of the FC_Li over time in the same individual is such as to allow adequate characterization with one, or at most, two measurements.

Study 2 addressed the important problem of the confounding effect of dietary sodium intake on FC_Li. While the subjects participating in the study of variability were free-living and on unrestricted diet, the participants in study 2 were investigated under metabolic ward con-
ditions. Thus, they were presumably in a steady-state condition with regard to their sodium balance when the $FCL_i$ was determined at the end of each experimental period. Under these controlled conditions, the effect of wide changes in sodium intake on the $FCL_i$ could be fully appreciated and was found to be quite remarkable. There was a stepwise increase in the average $FCL_i$ of these subjects with increasing sodium intake. Six out of eight subjects had their lowest value of $FCL_i$ on a sodium intake of 40 mmol/day, their highest level on the highest (210 mmol/day) sodium intake and an intermediate value on a sodium intake of 125 mmol/day, suggesting a continuous relation between these two variables. It is not possible from our data to assess whether this was a linear relation, as only three points were available for each subject. Nevertheless, it was noted that, on reducing sodium intake by 85 mmol from 125 to 40 mmol/day, a decrease in $FCL_i$ of an average of 4.7 percentage points was observed, whereas on increasing sodium intake by a similar amount from 125 to 210 mmol/day, $FCL_i$ rose on average by only 3.2 percentage points; this finding suggests that for equivalent absolute changes the confounding effect of varying dietary sodium intake might be more important in the lower part of the distribution of dietary sodium values.

Our results with regard to the effect of sodium intake on $FCL_i$, are in agreement with those of Tomsen & Schou [2] and Solomon et al. [14] in man and those of Biollaz et al. [15] in Wistar rats, as well as with the clinical observation that sodium depletion after prolonged diuretic treatment is associated with reduced $FCL_i$ [16]. In their recent work addressing this subject, Roos et al. [17] did not detect a significant effect of changes in sodium intake on the $FCL_i$; however, at variance with our study, the authors measured the lithium clearance during heavy water loading and obtained, in general, unusually high clearance values compared with those previously reported in the literature [2, 16] and with our own. The authors themselves recognized that water loading apparently enhances lithium excretion, particularly so during marked sodium restriction [17]. It is possible that standardization of dietary sodium intake might further reduce the intra-individual variability of $FCL_i$, so improving the discriminating ability of the test.

Study 3 addressed a fundamental question with respect to the reliability of this test in the study of proximal tubule sodium handling; namely, whether lithium per se, at the dosage used for the determination of $FCL_i$ in man, would impair the renal handling of electrolytes. Controversial data have been published in this regard, most studies reporting the effects of prolonged lithium treatment, which is known to induce nephrogenic diabetes insipidus [18, 19]: in some of these studies, a depressant action of lithium on tubular function was described [20] and contrasting effects have been found on sodium [21–31], potassium [24–27, 32] and calcium [20, 24, 28, 29, 32, 33–35] excretion, probably depending on different experimental conditions. In the recent systematic study by Thompson et al. in Wistar rats [36], the acute intraperitoneal injection of a large dose of lithium (3.5 mmol/kg body weight) induced an obvious increase in water, sodium, potassium and calcium excretion which lasted for at least 16 h. In this and previous studies, the effects of lithium on tubular electrolyte handling appeared to be a direct function of plasma lithium concentration.

Our procedure for determination of $FCL_i$ was standardized with the use of 300 mg of lithium carbonate (equivalent to 8.1 mmol of elemental lithium): at this dosage, the plasma lithium concentration 11 h after lithium administration ranged in 90% of the cases between 0.10 and 0.17 mmol/l, a concentration ten times lower than that associated with pharmacological and possibly toxic effects (1–1.5 mmol/l). The data obtained from our study of a group of subjects placed on a fixed sodium diet indicated that the consumption of 8.1 mmol of lithium did not have any effect on sodium, potassium and calcium fractional clearance measured between 9 and 13 h after the dose, strongly suggesting that tubular function is not depressed by such a small lithium dose and then that the ‘true’ sodium delivery out of the proximal tubule is being measured under these experimental conditions.

Likewise, the findings of study 4 clearly indicated that lithium administration had no effect on several biochemical indicators of kidney and liver function as well as on metabolic indices which are often investigated in epidemiological surveys, indicating that the concomitant evaluation of these parameters is feasible and not at all impaired by the concomitant determination of the $FCL_i$.

In conclusion, the methodological studies presented here suggest that there may be a good potential for the use of $FCL_i$ in clinical and epidemiological investigation: its determination is safe, relatively simple and, at least when a low lithium dose is administered, it is not associated with significant derangement of tubular function. Our data indicate that even with a single measurement made under free-living conditions, the diminution of the correlation coefficient between $FCL_i$ and an other given variable due to its intra-individual variation is relatively low and acceptable in most cases. Our data also suggest that much of the intra-individual variation of $FCL_i$ measured under free-living conditions on unrestricted diet may be traced to day-to-day variability in sodium intake. In those individuals who vary their day-to-day sodium intake to a large extent, this problem may become important. Thus, to further improve the discriminating ability of the test, the sodium intake should be standardized. Other likely sources of intra-individual variation are the recent consumption of certain drugs (i.e. diuretics, methylxanthines and probably others), performance of vigorous physical exercise during the test and changes in posture. These factors were all under control in our study, but, if not taken care of, they might add additional sources of intra-individual variation.

REFERENCES

Lithium clearance: a methodological assessment


