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Determinants of the renal clearance of exogenous lithium in a large sample of a white male working population

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1. The associations between the renal clearance of ingested lithium (used as a marker of renal proximal tubular sodium handling) and a number of biological variables have been investigated in an unselected sample of 592 healthy and untreated white men (aged 21–68 years) under their usual living conditions and drawn from a population at work.

2. Renal excretion of lithium was expressed both as clearance of lithium and as fractional excretion of lithium, i.e. normalized for unit of glomerular filtrate.

3. Clearance of lithium was positively associated with a number of anthropometric variables such as weight ($r=0.215$; $P<0.001$), height ($r=0.212$; $P<0.001$), body mass index ($r=0.122$; $P<0.01$) and body surface area ($r=0.244$; $P<0.001$). However, when expressed as fractional excretion of lithium many of these associations were lost or tended to be negative (weight, $r=-0.107$, $P<0.01$; body mass index, $r=-0.119$, $P<0.01$), greatly depending on the strong relationship between body size and/or mass and glomerular filtration rate. The associations between clearance of lithium and other renal variables reflected, in part, a spurious association mediated by the common relationship with glomerular filtration rate. However, when expressed as fractional excretion of lithium, only some associations were apparent (fractional excretion of sodium, $r=0.256$, $P<0.001$; fractional excretion of uric acid, $r=0.336$; $P<0.001$), probably indicating some plausible biological relationships. These results were confirmed by analysis of co-variance by quintiles of clearance of lithium and fractional excretion of lithium.

4. The results of the present study show that the renal excretion of ingested lithium (an approximate index of proximal tubular sodium handling in man) could be used in an epidemiological setting. However, the use of the fractional excretion of lithium rather than the clearance of lithium as such would be advisable to remove the confounding effects of age and anthropometry, at least in a white middle-aged male working population.

INTRODUCTION

It has been suggested that the measurement of the renal clearance of lithium after oral administration of a small dose of lithium could represent a non-invasive method for the assessment of sodium reabsorption from proximal and distal segments of the nephron in man [1, 2]. This offers a unique opportunity to delineate the segments of the nephron at which reabsorption of sodium occurs in man. The technique has already been employed in man for physiological, pathophysiological and pharmacological studies, although it is not free from potential limitations (for a review, see [3]).

Sodium reabsorption is a dynamic process and the renal clearance of lithium may be dependent on a number of variables and factors which can either directly modify it or merely be associated with it. Therefore, it is important that the determinants of the renal clearance of lithium are fully understood and that the possible biological correlates are investigated as the interpretation of results using the renal clearance of ingested lithium as an index of proximal tubular sodium handling could be influenced by them. This issue was addressed by Schou et al. [4] in a limited group of psychiatric patients on long-term treatment with lithium. However, owing to the highly selected group of patients studied, their conclusions are difficult to extend to a more general and healthy population.

We therefore studied the possible determinants of the renal clearance of ingested lithium among a number of biological variables in a large sample of healthy and untreated white men under their usual living conditions drawn from a population at work.

EXPERIMENTAL

Population

The study was carried out in Pozzuoli, a suburban area of Naples, at the Olivetti factory where mainly male workers are employed. It was part of the 10-year follow-up of a nationwide survey on the

Key words: epidemiology, lithium clearance, renal tubular function, sodium handling.

Abbreviations: BMI, body mass index; C_x, clearance of x; FE_x, fractional excretion of x.

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prevalence of cardiovascular risk factors sponsored by the National Research Council (CNR ATS-RF2) and started in 1976–77 [5–10]. Between April 1987 and May 1988 a sample of 783 white males (age range 21–68 years) were seen who represented the male work force currently employed at the time of the study [11]. Six hundred and eighty-eight of them (87.9%) had blood tests performed and 61 of them were then excluded as they were on pharmacological treatment known to affect the renal lithium clearance [3]. Six hundred and twenty-seven untreated males were then asked to provide a timed urine collection and were included in the final analysis. In 35 cases urine collections were not suitable for analysis because they were admittedly incomplete or missing. Therefore, complete sets of data were finally available for 592 participants.

The examinations were carried out in the morning, with the participants fasted, in a quiet and comfortable room within the factory premises; the participants were allowed to go about their normal activities but were discouraged from vigorous exercise and were asked to abstain from smoking and not to drink alcohol, coffee or other caffeine-containing drinks in the morning of the study. The study was approved by the local Ethics Committee and included a physical examination, a resting ECG, a blood test and a timed urine collection.

Protocol

Age was recorded at the last birthday. Body weight and height were measured on a standard beam balance scale with an attached ruler, with the participants wearing indoor clothing and no shoes. The body mass index (BMI) was calculated as the weight/height^2 ratio (kg/m^2). Body surface area was calculated as weight$^{0.425}$ × height$^{0.725}$ × 71.84 [12]. Blood pressure was measured between 08.00 and 11.00 hours after the participant had been sitting upright for at least 10 min. Systolic and fifth phase diastolic blood pressures were measured three times 3 min apart with a random zero sphygmomanometer (Gelman Hawksley Ltd) [13] and appropriate cuff size by trained observers who had attended blood pressure training sessions for standardization of the reading procedure. The first reading was discarded and the average value of the last two measurements for both systolic and diastolic pressure was recorded.

A questionnaire was administered by one trained observer who was unaware of the participants' blood pressure and other clinical characteristics. The questionnaire was designed to gather information on socioeconomic status, lifestyle, dietary habits and family history of vascular diseases. Smoking information was gathered to permit classification of subjects as non-smokers (if they had never smoked), ex-smokers (if they had stopped for at least 6 months) and current smokers. Each subject was also asked to report his alcohol intake during the week preceding the interview, specifying three types of alcoholic beverages, table wine, beer and spirits. The participants were then grouped as non-drinkers (group I) and drinkers, and the latter were classified in four categories by increasing daily consumption of table wine (group II, one glass/day; group III, one–two glasses/day; group IV, 0.5 litre/day; group V, 1 litre or more/day), since this was, by and large, the prevalent type of alcoholic beverage consumed. The total daily amount of ethanol ingested was also estimated individually, using updated food tables of the Italian Institute of Nutrition (1980), with the absolute ethanol content taken as being 11% by volume for table wine, 3.5% for beer and 30% for spirits.

A fasting timed urine collection was obtained from each participant on the morning of the examination, the volume and length of the collection were recorded and specimens were taken for electrolytes, creatinine and uric acid determinations. Creatinine clearance (C_{Cr}) was taken as an index of glomerular filtration rate and also corrected for body surface area (C_{Cr}/body surface area). Urinary creatinine was measured by the picric acid colorimetric method, urinary electrolytes by an ion-selective electrode (Beckman Electrolyte, EA2) and uric acid by an enzymic colorimetric method (Seragen Diagnostics). The average collection time was 208 ± 43 min (mean ± SD) and the average volume was 309 ± 180 ml ($n = 592$).

Venous blood was taken without stasis in men who had been sitting upright for 10 min between 08.00 and 11.00 hours, after the blood pressure measurements, at the mid-point of the urine collection for determination of serum electrolyte, urea, creatinine and uric acid concentrations. Serum creatinine was measured by the picric acid colorimetric method, electrolytes by an ion-selective electrode (Beckman Electrolyte, EA2) and uric acid by an enzymic colorimetric method (Seragen Diagnostics).

Exogenous lithium clearance

Following detailed written instructions, on the day before the visit, the participants consumed their evening meal at no later than 19.00 hours and took a 300 mg of lithium carbonate capsule (Carbolithium, IFI), delivering 8.1 mmol of elemental Li, at 22.00 hours. On the morning of the study, a fasting timed urine collection was performed (see above) and the urinary lithium concentration was measured. At the mid-point of the urine collection, a blood sample was obtained by venepuncture without stasis (see above) for determination of serum lithium concentration. Urinary and serum lithium were determined by atomic absorption spectrophotometry. Preliminary studies [14] of serum lithium kinetics, performed under experimental conditions similar to those of the present study, have shown linearity ($r = -0.99$) of the log serum lithium concentration on time between 9 and 17 h after a

300 mg of lithium carbonate dose, a finding which allowed the determination of the lithium clearance using a single value of serum lithium concentration measured at the mid-point of the urine collection. A methodological assessment performed in our laboratory on the variability of the fractional lithium excretion, determined by multiple measurements repeated several days apart in free-living white subjects on an unrestricted diet, has provided intra- and inter-individual coefficients of variation of 8.5% and 14.7%, respectively, with a ratio of intra-individual to inter-individual variance of 0.33, low enough to permit satisfactory characterization of an individual in a population with a single measurement [14]. Similar results have also been reported by Boer et al. [15].

Standard formulae were used to calculate the clearances (ml/min) of creatinine (C_{Cr}), sodium (C_{Na}), potassium (C_K), uric acid (C_{UrAc}) and lithium (C_{Li}) and the fractional excretions (%) of sodium (FE_{Na}), potassium (FE_K), uric acid (FE_{UrAc}) and lithium (FE_{Li}). Since C_{Cr} measures the input of fluid to the proximal tubules and C_{Li} measures the fluid delivered to the loop of Henle, it is possible to calculate the fraction of fluid (and sodium) which is not reabsorbed (i.e. fractional excretion, $FE_{Li}=C_{Li}/C_{Cr}$) by the proximal tubule. If C_{Li} is a measure of fluid entering the loop of Henle from the proximal tubule, it is also possible to assess sodium reabsorption in more distal parts of the nephron (loop of Henle, distal tubule and collecting ducts); it is, therefore, possible to calculate the FE_{Na} (C_{Na}/C_{Li}) by distal segments.

Statistical analysis

Results are expressed as means and SDs. The Kolmogorov–Smirnov test was used to determine whether frequency distributions significantly shifted from a normal Gaussian curve. When values were not normally distributed and their frequency distribution curves were significantly shifted from a Gaussian curve, log transformation of values was also used in the analysis. χ^2 cross-tabulation statistics were used to test differences in the frequencies of smoking and habitual wine consumption. Associations were studied by both analysis of variance across quintiles of renal lithium clearance and by Pearson's correlation analysis. To allow for confounders, both analysis of co-variance across quintiles of renal lithium clearance and partial correlation analyses were used. The level of statistical significance was set at 0.01 or less for a two-tailed P value using Bonferroni's method.

RESULTS

Characteristics of the population sample

The population sample ($n=592$) had a mean age of 46.3 ± 7.4 years, a body weight of 73.9 ± 9.9 kg, a BMI of 26.1 ± 3.0 kg/m^2, a body surface area of 1.83 ± 0.13 m^2 and a blood pressure of $125.5/86.2\pm15.5/9.8$ mmHg (systolic range 91–198 mmHg and diastolic range 60–124 mmHg). The mean serum creatinine concentration was 96.6 ± 9.4 μmol/l and none of the participants had a serum creatinine concentration >165 μmol/l. The mean serum lithium concentration was 0.135 ± 0.032 mmol/l and the mean serum uric acid level was 0.308 ± 0.060 mmol/l. More than half (55.6%) of the participants were current smokers, 26.8% had stopped and only 17.7% had never smoked. The large majority (89.0%) of men were habitual table-wine drinkers and 8.6% were heavy drinkers (more than 1 litre of wine/day).

Table 1. Characteristics of renal function in the entire sample of 592 untreated white male workers. Abbreviation: UFR, urine flow rate.

	Mean	SD
C_{Cr} (ml/min)	98.5	21.6
C_{Cr}/body surface area (ml min m^2)	53.6	10.8
C_{Na} (ml/min)	1.01	0.42
C_K (ml/min)	12.1	5.9
C_{Li} (ml/min)	23.3	6.7
C_{UrAc} (ml/min)*	8.2	3.4
FE_{Na} (%)	1.04	0.39
FE_K (%)	12.4	5.6
FE_{Li} (%)	23.8	5.0
FE_{UrAc} (%)	8.4	2.9
UFR (ml/min)	1.52	0.95
C_{Na}/C_{Li} (%)	4.5	1.8

*$n=568$.

Table 1 shows the characteristics of renal function in the entire population sample. The frequency distribution of FE_{Li} showed a normal Gaussian curve (Kolmogorov–Smirnov test: $z=1.27$, $P=$not significant) with a mean value of 23.8 ± 5.0% (range 9.6–39.5%).

Relationships between exogenous lithium clearance and age, anthropometry and blood pressure

Pearson's correlation analysis was first carried out to determine the degree of association between both C_{Li} and FE_{Li} and age, anthropometry and blood pressure (Table 2). C_{Li} was inversely related to age and directly related to anthropometric indices such as body weight, BMI and body surface area, whereas no significant relationship was found with both systolic and diastolic blood pressure. However, when expressed as FE_{Li}, a parameter which indicates the amount of lithium excreted per unit of filtrate, most of the relationships were lost and, if anything, body weight and BMI became both inversely related to it. This indicates that, as C_{Li} by itself is dependent on the glomerular filtration rate (C_{Li} related to C_{Cr}: $r=0.689$, $P\ll0.001$) and as BMI and age are both predictors of glomerular filtration rate

Table 2. Relationships between lithium excretion and age, anthropometry and blood pressure in the entire sample of 592 untreated white male workers. Results are expressed as correlation coefficients. Statistical significance: *$P<0.01$, **$P<0.001$. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

	C_{Li} (ml/min)	FE_{Li} (%)
Age (years)	−0.137**	0.057
Height (cm)	0.212**	−0.002
Weight (kg)	0.215**	−0.107*
BMI (kg/m²)	0.122*	−0.119*
BSA (m²)	0.244**	−0.082
SBP (mmHg)	0.009	−0.010
DBP (mmHg)	0.011	−0.040

($r=0.274$, $P<0.001$ and $r=-0.243$, $P<0.001$ versus C_{Cr}, respectively), FE_{Li} should be used instead of C_{Li} in order to remove the confounding effect of age and anthropometry.

To study the shape of these relationships, we looked at the associations by quintiles of both C_{Li} and FE_{Li} (Fig. 1). Some of the associations with C_{Li} did not appear to be linear (i.e. height, weight, body surface area). However, when expressed by quintiles of FE_{Li}, a different picture emerged in line with the results of the correlation matrix, indicating the confounding role of age and anthropometry in the evaluation of C_{Li}.

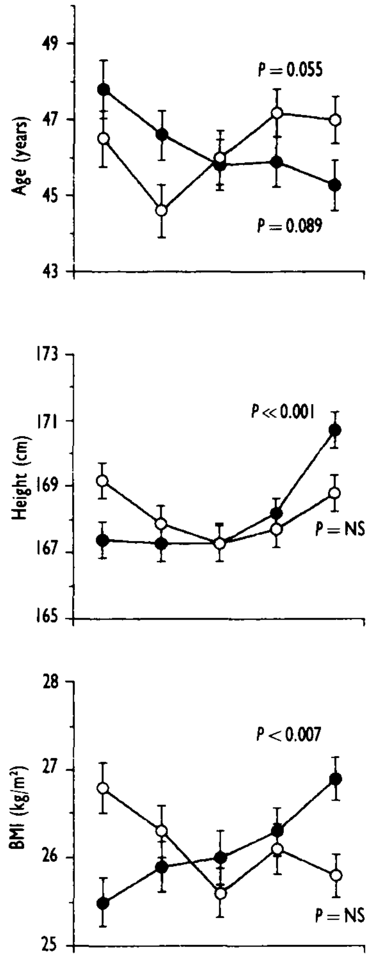

Fig. 1. Age and anthropometry by quintiles of both C_{Li} (●) and FE_{Li} (○). There are over 100 participants in each quintile. Results are means and SEM. Statistical analysis is by analysis of variance. Abbreviation: NS, not significant.

Relationship between exogenous lithium clearance and smoking habit and habitual wine consumption

There was no difference in the proportion of smokers by quintiles of both C_{Li} and FE_{Li} ($\chi^2=0.07$, $P=0.80$ and $\chi^2=0.72$, $P=0.40$, respectively). Likewise, there was no association between wine consumption and both C_{Li} and FE_{Li} ($\chi^2=1.08$, $P=0.30$ and $\chi^2=0.72$, $P=0.40$, respectively).

Relationships between exogenous lithium clearance and renal parameters

As mentioned above, C_{Li} was strongly related to C_{Cr} (Table 3), thereby also showing significant associations with C_{Na}, C_K and C_{UrAc}. However, using FE_{Li} as an index of lithium excretion, it became evident that although FE_{Na} and FE_{UrAc} were indeed associated with FE_{Li}, FE_K was not (Fig. 2). The results did not vary when both analysis of covariance or partial correlation matrices were computed after adjustments for age and anthropometry (Table 4).

Table 3. Relationships between lithium excretion and renal parameters in the entire sample of 592 white male workers. Results are expressed as correlation coefficients. Statistical significance: *$P<0.01$, **$P<0.001$.

	C_{Li} (ml/min)	FE_{Li} (%)
C_{Cr} (ml/min)	0.689**	−0.105
C_{Cr}/body surface area (ml min⁻¹ m⁻²)	0.653**	−0.090
C_{Na} (ml/min)	0.472**	0.176**
C_K (ml/min)	0.275**	0.012
C_{UrAc} (ml/min)†	0.555**	0.228**
FE_{Na} (%)	0.110*	0.256**
FE_K (%)	−0.033	0.073
FE_{UrAc} (%)†	0.210**	0.336**

†n = 568.

DISCUSSION

The aim of the present study was to investigate the biological determinants of the renal clearance of exogenous lithium in man and to consider some important methodological aspects for application and interpretation in epidemiological studies.

To our knowledge, this is the first study of this kind in a large sample of a healthy population

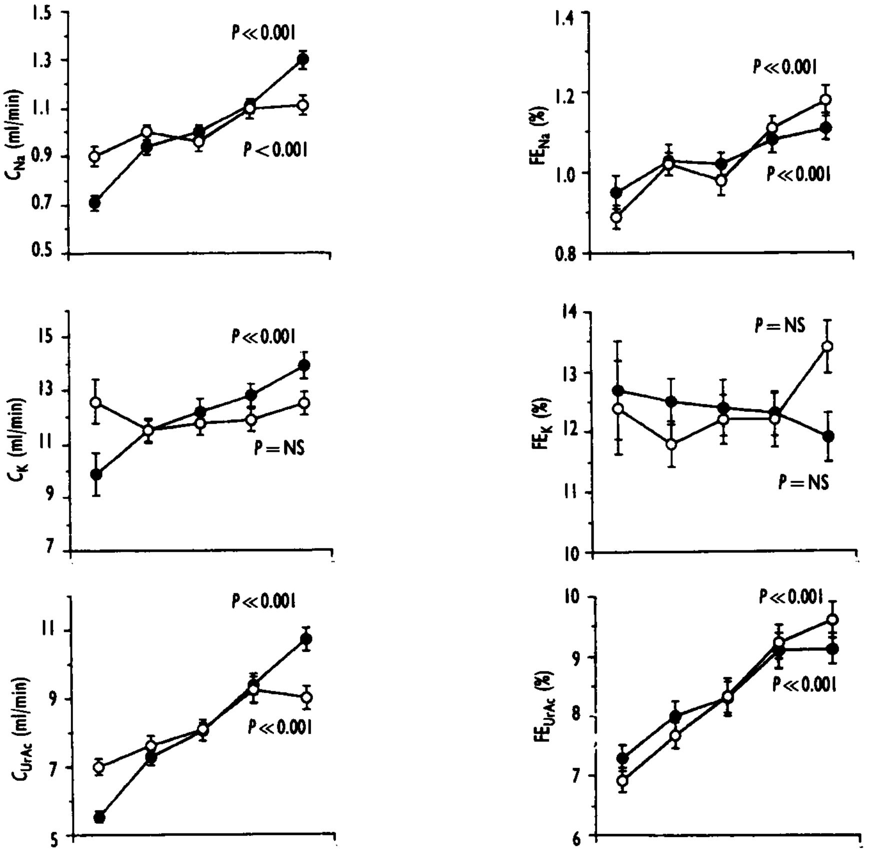

Fig. 2. Clearances and fractional excretion of sodium, potassium and uric acid by quintiles of both C_{Li} (●) and FE_{Li} (○). There are over 100 participants in each quintile. Results are means and SEM. Statistical analysis is by analysis of variance. Abbreviation: NS, not significant.

Table 4. Relationship between lithium excretion and blood pressure and renal parameters after adjustments for age and anthropometry in the entire sample of 592 untreated white male workers. Results are expressed as partial correlation coefficients. Statistical significance: *$P<0.01$, **$P<0.001$. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

Co-variates...	C_{Li} (ml/min)		FE_{Li} (%)	
	Age and BMI	Age and body surface area	Age and BMI	Age and body surface area
SBP (mmHg)	0.020	0.008	0.001	−0.019
DBP (mmHg)	−0.013	−0.030	−0.027	−0.049
C_{Cr} (ml/min)	0.679**	0.659**	−0.058	−0.068
C_{Cr}/body surface area (ml min m²)	0.640**	0.653**	−0.067	−0.075
C_{Na} (ml/min)	0.465**	0.452**	0.198**	0.195**
C_K (ml/min)	0.253**	0.237**	0.037	0.031
C_{UrAc} (ml/min)†	0.545**	0.536**	0.254**	0.252**
FE_{Na} (%)	0.133*	0.140**	0.250**	0.251**
FE_K (%)	−0.030	−0.029	0.074	0.072
FE_{UrAc} (%)†	0.235**	0.243**	0.332**	0.333**

†$n=568$.

group under habitual living conditions. The results of this study clearly show that lithium clearance is significantly related to a number of biological variables. Correlation coefficients of 0.20–0.30 from cross-sectional studies may not seem impressive, but they can, nevertheless, indicate important biological relations. One reason for this is that most studies, including the present one, rely on measurements of the variables on a single occasion. Such measurements are subject to fluctuations due to the measurement process (random error) and to temporary deviations from an individual's usual value (intra-individual variation). Because of the diluting effects of such fluctuations, estimates based on single measurements will underestimate the real association between the level of 'usual' FE_{Li} and the value of any co-variate. This implies that the association detected may be stronger than observed.

Anthropometry appears to be an important determinant of C_{Li}. Body weight, BMI, height and body surface area are all positively and significantly associated with C_{Li}. However, when the clearance of lithium is expressed as FE_{Li}, many of these relationships are lost. This indicates that C_{Cr} is an important determinant of C_{Li} and that some of the variables are associated with C_{Li} merely because they are physiologically related to a common factor, i.e. the glomerular filtration rate.

A similar interrelationship may explain the confounding effect of age. Age is inversely associated with C_{Li} and this reflects, at least in part, the physiological fall in the glomerular filtration rate with ageing [16]. When expressed per unit of filtrate, thereby being independent of the volume and time of the collection, the renal excretion of lithium is no longer associated with age, suggesting that the fractional delivery of fluid and sodium from the proximal to the distal tubule is independent of age. This is in agreement with previous findings in psychiatric patients on long-term lithium treatment [4].

We also found that C_{Li} was associated with C_{Na}, C_K and C_{UrAc}. However, when expressed as FE_{Li}, the relationship with C_K disappeared whereas those with C_{Na} and C_{UrAc} were strengthened. The relationship between FE_{Li} and FE_{Na} is not surprising. Alterations in sodium intake induce respective changes in FE_{Li} [14, 17–19], reflecting the change in the amount of filtered load of sodium which escapes reabsorption at the proximal site. In our study, participants were not asked to alter their dietary habit; the relationship between FE_{Na} and FE_{Li}, therefore, seems to reflect, in greater part, the difference in sodium intake within the population, i.e. a greater FE_{Li} in those on a higher sodium intake. A strong and direct relationship was also seen between FE_{Li} and FE_{UrAc}. The renal handling of uric acid is a complex sequence of tubular reabsorption and secretion occurring almost exclusively at the proximal site [20]. This relationship would suggest that, at least in part, uric acid and lithium (or sodium) reabsorption at the proximal tubule might share a common pathway. This view is supported, though indirectly so, by the finding that, in a sub-sample of the same population, moderate sodium restriction induces a significant reduction in FE_{UrAc} along with the expected reduction in both FE_{Na} and FE_{Li} [21].

The clearance of exogenous lithium as an approximate index of proximal renal tubular handling of sodium, as mentioned earlier, is not free from potential limitations [3]. One possible confounding factor affecting the clearance of lithium through either changes in glomerular filtration rate or changes in renal haemodynamics is posture. It has been suggested that the renal excretion of lithium may be increased when the patient is in the supine position as compared with the standing position [22]. In our study the primary aim was to look at the biological associations as they occur during daily normal life. Participants were ambulant during their clearance time and were engaged in light or sedentary activities. This would have, if anything, increased the variability, thus making any 'true' relationship more difficult to demonstrate and underestimating the 'true' strength. On the other hand, we feel it is unlikely that the lack of standardized posture itself, without any systematic error, could explain the findings in the present study.

It has also been shown that administration of a single oral dose of lithium can cause natriuresis [23] and this effect could invalidate some of the assumptions on which its interpretation is based [1]. This effect, however, is dose-dependent and it is not detected using 300 mg of lithium carbonate, as employed in the present study.

Finally, it has been suggested in animal studies [24] that on a very low sodium intake some distal handling of lithium occurs. Studies in man, however, have failed to confirm this [4], suggesting important species differences in the physiological renal handling of lithium. In our study none of the participants was on a very low sodium intake (i.e. <50 mmol/24 h), thus ruling out this potential bias from our findings.

The validity of the clearance of exogenous lithium as an approximate index of renal proximal tubular handling of sodium was tested in a sub-sample of 57 men (about 10% of the total sample) who agreed to undergo 3 days of moderate sodium restriction, to have the clearance study repeated and to provide complete 24 h urine collections. Sodium excretion was reduced from 183.6 ± 58.2 ($\pm$SD) to 69.8 ± 33.6 mmol/24 h ($P<0.001$). FE_{Li} was also reduced from 24.6 ± 5.4 to $19.6 \pm 5.5\%$ ($P<0.001$). The changes were of the same order of magnitude as those achieved in our preliminary methodological assessment [14] and were in line with results obtained in more controlled experimental conditions [17–19].

In conclusion, the present study of a large sample of healthy and untreated white male workers shows that the renal excretion of lithium (approximate index of proximal tubular sodium handling in man) could be used in an epidemiological setting. However, the use of the fractional excretion of lithium rather than the clearance of lithium would be advisable to remove the confounding effect of age, body size and anthropometry, all dependent on the common relationship with the glomerular filtration rate. However, whether this holds in women or in different ethnic groups is as yet to be confirmed. The wider use of this simple technique at population level may help investigate some conditions in which an altered tubular sodium handling has been suggested [25, 26]. The alternative use of the clearance of endogenous lithium, recently become available [27–29], subject to proper validation, could be of additional value, particularly for large epidemiological studies.

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