Effect of a single test dose of lithium carbonate on sodium and potassium excretion in man


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SUMMARY

Key words: lithium, plasma renin activity, potassium excretion, sodium excretion.

1. The possible natriuretic and kaliuretic effects of a single dose of lithium, as used in lithium clearance studies, were investigated in 15 healthy subjects on fixed sodium (100 mmol/24 h) and potassium (70 mmol/24 h) intakes. Lithium carbonate (300 mg or 600 mg) or placebo tablets were administered, double-blind and in random order, midway through a 48 h urine collection (divided into six 8 h periods), at 23.00 hours.

2. During the three 24 h periods which preceded the administration of lithium or placebo (control days), rates of sodium and potassium excretion followed normal circadian patterns, but no differences in excretion rates between the 3 control days were observed. Placebo tablets did not affect excretion rates.

3. After the 300 mg dose of lithium carbonate, 24 h sodium excretion increased by approximately 17 mmol (P<0.05); almost all of the natriuretic effect occurred during the first two 8 h periods. No effect on potassium excretion was observed.

4. After the 600 mg dose of lithium carbonate, 24 h sodium excretion increased by approximately 48 mmol (P<0.001) and 24 h potassium excretion increased by approximately 19 mmol (P<0.01). These effects were confined to the first two 8 h periods and thus occurred before and during the usual lithium clearance period.

5. Plasma renin activity, measured in 10 subjects, increased after the 600 mg dose of lithium carbonate (P<0.005), but plasma concentrations of aldosterone and atrial natriuretic peptide were not significantly affected. Neither the 300 mg dose of lithium carbonate nor the placebo tablets affected hormone levels.

6. It is recommended that the test dose of lithium carbonate for use in lithium clearance studies should not exceed 300 mg.

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status was also assessed. The objective was to identify, if possible, a suitable test dose of lithium for use in lithium clearance studies.

METHODS

A double-blind study was performed on 15 healthy, normotensive individuals (nine male, six female), aged 19–42 years. Written informed consent was obtained from each subject and the study was approved by the Hospital Ethical Committee. The experiments were conducted over three 5-day periods separated by intervals of at least 2 days. Under the supervision of the Metabolic Unit dietitian, the subjects adhered to a diet containing 100 mmol of sodium and 70 mmol of potassium/day throughout each 5-day period. The subjects were instructed to avoid alcohol. They followed their normal daily activities, but strenuous exercise was avoided. Urine was collected for the final 48 h of each 5-day period; collections were divided into six 8 h periods, from 23.00 hours on day 3 to 23.00 hours on day 5. The intake of tea and coffee during the final 48 h was standardized for each subject. On day 4, at 23.00 hours, subjects took either lithium carbonate (Priadel; Delandale Laboratories, Canterbury, Kent, U.K.) or matched placebo tablets. The dose of lithium carbonate was 300 mg (8.1 mmol of Li) or 600 mg (16.2 mmol of Li). The three treatments were assigned in random order.

In ten subjects, venous blood samples (50 ml) were taken, after 10 min sitting, on days 4 and 5 between 09.00 hours and 11.00 hours.

Urinary sodium and potassium concentrations were measured by flame photometry (model 543; Instrumentation Laboratory, Warrington, Cheshire, U.K.), and plasma lithium concentrations by atomic absorption spectroscopy (model 151; Instrumentation Laboratory). Ria was used to measure plasma renin activity (PRA) [8] and the plasma concentrations of aldosterone [9] and (after Sep-Pak extraction) atrial natriuretic peptide (ANP) [10].

Results are presented as means ± SEM. Statistical analysis was by analysis of variance with repeated measures. Where significant differences were found by using analysis of variance, paired measurements (control day versus treatment day) were then compared by using the least significant difference derived from the pooled error variance. Because of skew of the data for plasma hormone measurements, these results were assessed by using Wilcoxon's signed ranks test for matched pairs (control day versus treatment day). Results are reported as significant when the level of significance was P<0.05 in a two-tailed test.

RESULTS

Comparison of control days

On each of the 3 control days that preceded administration of lithium carbonate or placebo, excretion of sodium and potassium followed normal circadian rhythms (see Fig. 2), with higher excretion rates during periods 2 (07.00–15.00 hours; P<0.001 for each cation) and 3 (15.00–23.00 hours; sodium, P<0.05; potassium, P<0.01) than during period 1 (23.00–07.00 hours). However, there was no significant time effect for urine volume.

Excretion of electrolytes and water did not differ between the 3 control days, either for the total 24 h collection or for individual 8 h periods.

Effect of lithium

Twenty-four hour excretion rates (Fig. 1). Administration of placebo tablets had no discernible effect on the
Effect of lithium on electrolyte excretion

Effect of lithium on electrolyte excretion

excretion of sodium, potassium or water. However, after the 300 mg dose of lithium carbonate, sodium excretion increased in 11 out of 15 subjects (mean 24 h increase compared with control day = 17 mmol, \( P < 0.05 \)). Although the natriuresis appeared to be accompanied by a moderate increase in urine volume, this was not statistically significant over the 24 h period. Potassium excretion was unaffected.

After the 600 mg dose of lithium carbonate, sodium excretion increased in 14 out of 15 subjects (mean 24 h increase compared with control day = 48 mmol, \( P < 0.001 \)). Urine volume also increased significantly, as did potassium excretion.

Eight hour excretion rates (Fig. 2). Placebo tablets had no effect on excretion rates during any of the 8 h periods. After the 300 mg dose of lithium carbonate, sodium excretion appeared to increase during the first two 8 h periods (periods 1 and 2) as compared with the corresponding periods of the control day, but the changes were not statistically significant. Urine volume increased significantly during period 1.

The 600 mg dose of lithium carbonate resulted in significant increases in the excretion of sodium, potassium and water during periods 1 and 2; excretion rates had returned to normal by period 3.

Plasma hormone and lithium concentrations. There were no significant differences in values for PRA, aldosterone or ANP between the 3 control days (Table 1). Neither placebo tablets nor the 300 mg dose of lithium carbonate significantly affected the plasma concentration of any of the hormones. After 600 mg of lithium carbonate, PRA was increased, but there was no significant change in the plasma concentrations of aldosterone or ANP.

Plasma lithium concentrations, 10–12 h after ingestion of the 300 mg and 600 mg dose of lithium carbonate, were 120 ± 10 and 241 ± 23 μmol/l, respectively.

DISCUSSION

The use of the lithium clearance method to provide an estimate of end-proximal fluid delivery has gained increasing popularity in recent years. Although concerns over its specificity have been expressed (see [1]), there is little doubt that it remains the best method available for assessment of proximal tubular function in man. A further
Thus the absence of sodium retention after the initial usual test dose of lithium carbonate (600 mg) on sodium the sodium deficit, although no significant changes in the this period, PRA was also raised, possibly as a result of are consistent with a proximal tubular effect. In this spontaneous increases in sodium and potassium excretion fractional sodium reabsorption in proximal tubules imply that the lithium was no longer active. The normal excretion, amounting to some 50 mmol over a 24 h lithium may have persisted for up to 24 h.

The present results demonstrate a clear effect of the usual test dose of lithium carbonate (600 mg) on sodium excretion, amounting to some 50 mmol over a 24 h period. Effects on potassium excretion and urine volume were also observed (although since water intake was not standardized, the data for urine flow can give only qualitative information). Most of the effects occurred during the first and second 8 h periods, when plasma lithium levels will have been at their highest [11]; excretion rates returned to control values during the final 8 h period. Thus at the time when lithium clearance measurements would normally be performed, i.e. during the second 8 h period, a significant sodium loss had occurred and sodium excretion was still elevated. During this period, PRA was also raised, possibly as a result of the sodium deficit, although no significant changes in the plasma concentrations of aldosterone or ANP were observed. The restoration of normal sodium excretion rates during the final 8 h period does not necessarily imply that the lithium was no longer active. The normal response to acute sodium loss is activation of compensatory mechanisms and consequent sodium retention. Thus the absence of sodium retention after the initial natriuresis in the present study suggests that the effect of lithium may have persisted for up to 24 h.

Little is known about the mechanism(s) underlying the lithium-induced natriuresis. It is possible that chronic, therapeutic doses of lithium inhibit the action of aldosterone on the distal nephron [12, 13], but such an effect seems inconsistent with the kaliuresis observed in the present study after the 600 mg dose. Rather, the simultaneous increases in sodium and potassium excretion are consistent with a proximal tubular effect. In this context, a micropuncture study in rats has shown that large intravenous infusions of lithium lead to reduced fractional sodium reabsorption in proximal tubules [14], an effect which might result from inhibition of the sodium/proton antiport mechanism in the luminal membrane [15, 16].

After administration of the lower dose of lithium carbonate (300 mg), 24 h sodium excretion was only moderately elevated (by <20 mmol on average); again, the natriuresis appeared to be confined to the first two collection periods. Urine volume was also moderately increased during the first collection period. However, potassium excretion was not significantly affected, and the subjects’ endocrine profiles remained unaltered.

The findings from this double-blind, placebo-controlled study are broadly consistent with previous observations. Although Strazullo et al. [7] found no effect of 300 mg of lithium carbonate on sodium or potassium excretion in a group of hypertensive patients, their observations were confined to a 4 h period before lithium administration and therefore missed most of the critical period. Another study, published in abstract form only, found that a dose of 500 mg of lithium carbonate caused small but significant increases in the excretion of water, sodium and potassium, measured over a 12 h period immediately after administering the lithium [4], and a recently published letter has reported an increase in fractional sodium excretion after a 600 mg dose of lithium carbonate [17] (although the latter study could not provide quantitative information, since sodium intake was uncontrolled). Finally, Lee and co-workers [5, 6] have shown that, when given in the evening, 750 mg of lithium carbonate (a higher dose than that normally employed for clearance measurements) results in a significant natriuresis the next morning [5, 6]. No data were given for potassium excretion.

In the present study we have attempted to provide a more thorough assessment of the effect of lithium by monitoring excretion rates for 24 h after its administration, the lithium being taken at the time generally used in studies of lithium clearance. Our objective was to assess any changes in sodium and potassium balance which might occur during lithium clearance measurements, and to identify, if possible, a suitable dose of lithium for such studies. A further index of physiological status during the ‘normal’ clearance period was provided by assaying the principal hormones whose concentrations would be expected to be influenced by changes in sodium balance. Our results suggest that measurements of lithium clearance after administration of the ‘standard’ 600 mg dose of lithium carbonate should be interpreted with caution in view of the clear effect of this dose on sodium balance. On the other hand, the 300 mg dose, which still produces plasma lithium concentrations which can be measured accurately, caused only minor increases in sodium and water excretion and had no detectable effect on potassium excretion or endocrine status. Whilst any effect on sodium excretion is undesirable, it is likely that if the

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<td></td>
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<td>Li₂CO₃</td>
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<tr>
<td>PRA (pmol of Ang l⁻¹ ml⁻¹)</td>
<td>2.15 ± 0.34</td>
<td>2.21 ± 0.28</td>
<td>2.29 ± 0.29</td>
<td>2.69 ± 0.33</td>
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<td>Aldosterone (pmol/l)</td>
<td>682 ± 198</td>
<td>651 ± 146</td>
<td>594 ± 102</td>
<td>684 ± 115</td>
<td>694 ± 165</td>
<td>829 ± 192</td>
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<td>ANP (pg/ml)†</td>
<td>12.0 ± 3.0</td>
<td>13.5 ± 3.1</td>
<td>15.3 ± 5.7</td>
<td>13.8 ± 3.2</td>
<td>12.7 ± 3.0</td>
<td>13.0 ± 2.9</td>
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†Seven subjects only; values in three subjects were below the limit of sensitivity of the assay (3 pg/ml).

Table 1. Plasma hormone levels in 10 subjects on control and treatment days

Values are means ± sem. Statistical comparisons between treatment days and corresponding control days were made by using Wilcoxon’s signed ranks test for matched pairs: ⋆P < 0.005 compared with the corresponding control day.
lithium dose were reduced much further the plasma lithium concentration would approach the limits of precision of standard methodology (flame photometry or atomic absorption spectroscopy), thereby introducing an additional error into the clearance measurements. Ideally, endogenous lithium clearance should be measured, by using flameless atomic absorption spectroscopy [18]. However, until such measurements can be performed routinely with the same precision as those of exogenously administered lithium, we would recommend the use of lithium carbonate at as low a dose as possible, certainly not exceeding 300 mg, for future studies of lithium clearance.

REFERENCES
2. Thomsen, K. Lithium clearance as a measure of sodium and water delivery from the proximal tubules. Kidney Int. 1990; 37 (Suppl. 28), S10-16.