Renal function on and off lithium in patients treated with lithium for 15 years or more. A controlled, prospective lithium-withdrawal study

H. Bendz, I. Sjödin, and M. Aurell

Department of Psychiatry, University Hospital, Lund; Department of Psychiatry, University Hospital, Linköping; Department of Nephrology, University of Göteborg, Göteborg, Sweden

Abstract

Background. Controversy remains over the magnitude and reversibility of reduced renal function in long-term lithium patients.

Method. Thirteen patients with 18 years (range 15-24) on lithium discontinued the treatment, and were re-examined twice after 5 and 9 weeks (4-16) off lithium. They were compared to a non-lithium psychiatric control group, matched for age and sex.

Results. Glomerular filtration rate (GFR) tended to improve from 69 (39-96) to 74 (39-94) ml/min/1.73 m² BSA, P = 0.057, which was not significantly different from 78 (61-106 ml/min per 1.73 m² BSA in the controls. Reduced GFR was found in only two of the lithium patients off lithium, and in none of the controls. Maximal urinary concentrating capacity did not improve at all. It was 637 (130-875) mOsm/kg H2O in the lithium patients, which was lower than 856 (705-1.035) mOsm/kg H2O (P<0.01) in the controls. Two of the lithium patients had isosthenuria.

Conclusions. Lithium patients often have an irreversible, clinically important reduction of Umax, sometimes progressing to nephrogenic diabetes insipidus, while GFR is well preserved in most patients.

Key words: affective disorder; controlled study; hypercalcaemia; kidney function; lithium treatment; concentrating capacity; diabetes insipidus

Introduction

In 1977 Danish reports suggested that the well-known effects of lithium on renal function might not always be reversible as was commonly believed at the time [1]. Numerous studies that followed have resulted in conflicting conclusions as illustrated by recent reviews by Botton et al. [2], Schou [3], and Walker [4]. According to both Botton et al. and Walker, lithium treatment is a cause of progressive nephropathy sometimes ending in diabetes insipidus, while Schou states that with today's low-dose regimen, lithium does not cause irreversible kidney damage.

We have studied the magnitude and reversibility of reduced renal function in long-term lithium patients in 13 patients treated with lithium for almost two decades. Kidney function was studied both on and off lithium and compared to that of a group of psychiatric control patients, never treated with lithium.

Subjects and methods

Patients

The study took place between 1986 and 1989. The patients were recruited from a group of 142 patients studied cross-sectionally during ongoing lithium treatment [5]. Patients with ongoing lithium treatment for 15 years or more were included. The only additional criterion for inclusion in the withdrawal study was a low relapse risk. Each of the lithium patients was compared to a control patient who had a diagnosis of an affective disorder, who had never been treated with lithium (with one exception), and who was individually matched with the lithium patient for age and sex. After the conclusion of the study it was observed that one control patient had been treated with lithium on two occasions for about 8 weeks, 4 and 12 years previously. His renal function in this study was not reduced.

Serum lithium values were unreliable from the start of the treatment up to 1977, when the patients had been on lithium for an average of 10 (7-16) years. Therefore, average or maximal serum lithium over the duration of the patients' treatment could not be assessed. Instead, we registered maximal serum lithium and calculated average serum lithium over the year of 1978, and over the time period from 1979 up to this study. We also made use of the information on daily lithium dose which was available in six patients from the start of the treatment, and in another three patients from the 2nd, 3rd or 5th year of treatment, calculating 'first lithium dose', i.e. the average lithium dose over the 1st (2nd, 3rd or 5th) year of treatment, over the year of 1978, and over the duration of the treatment.

The lithium patients were examined three times, once during ongoing lithium treatment, and after 5 and 9 weeks...
off lithium. The control patients were examined only once. All participants were examined as outpatients.

A total of 13 lithium patients and 13 control patients gave informed consent according to the Declaration of Helsinki.

**Laboratory analyses**

Glomerular filtration rate (GFR; ml/min per 1.73 m²) was measured according to Bröchner-Mortensen [6] with reference values according to Granerus and Aurell [7]. Serum creatinine (μmol/l) was measured according to routine laboratory methods. Maximum urinary concentration capacity (Umax; mOsm/kg H₂O) was measured using the synthetic vasopressin analogue DDAVP after a 12-h overnight water deprivation period [8] with reference values according to Tryding et al. [9]. Urine volume (Uvol; ml/24 h) was the mean of three consecutive measurements. Polyuria was defined as Uvol > 3.000 ml/24 h. It was not measured in the controls. Serum lithium (mmol/l) and routine clinical chemistry were analysed according to standard methods.

**Statistics**

The paired t test, the Mann–Whitney test, and the Fisher exact test were employed. Missing data were responsible for the lower number than the actual number of patients. Statistical significance was set at P < 0.05, two-tailed. Results are presented as mean and range. Where appropriate, the median is given in parentheses after the mean.

**Ethics**

The study was approved in 1985 as a multicenter study by the Ethics Committee for Clinical Studies at the Karolinska Institute in Stockholm.

**Results**

**Clinical observations (Table 1)**

There were six female and seven male lithium patients. Their mean age was 59 (range 37–69) years. Their psychiatric disorder had lasted for a mean of 32 (19–42) years. When entering the study, five patients were on lithium only, seven were also on psychotropic and/or somatic medication. The mean lithium dose was 23 (16–32) mmol/24 h. The mean duration of the lithium treatment was 18 (15–24) years. One patient had a recorded episode of lithium intoxication. His GFR and Umax were normal. Four of the lithium patients had a diagnosis of cardiovascular disorder.

The mean age of the control patients was 59 (34–71) years. The mean duration of their psychiatric disorder was 20 (2–46) years which was significantly shorter than the lithium patients (P < 0.05). When entering the study, three of them were unmedicated, ten were on psychotropic and/or somatic medication. Four of the control patients had a diagnosis of cardiovascular disease.

There were no significant differences between the lithium-withdrawal patients and the background group of 142 patients, from which they were selected, in age, sex, psychiatric diagnosis, lithium treatment time, total cumulative lithium dose, average GFR and Umax, serum calcium, somatic morbidity, and number of hospitalizations. The withdrawal patients had spent less time in psychiatric hospital (Table 1).

**Laboratory analyses (Table 2)**

Renal function was studied once during lithium treatment and twice after an average of 5 and 9 weeks (range 4–16) off lithium.

- Mean serum lithium was 0.66 (0.30–0.90) mmol/l, and lithium was undetectable in all the lithium patients while off lithium and in all the controls.
- Average serum lithium in 1978 was 0.75 (0.45–1.03) mmol/l, and from 1979 up to this study 0.70 (0.57–0.83) mmol/l.
- Maximal serum lithium (data missing in one patient) from 1979 up to this study was below 1.0 mmol/l in seven of the patients while another four patients had occasional values above 1.0. One patient had three values above 1.0 mmol/l and a maximum value of 1.2 mmol/l.
- Average lithium dose/24 h. The first dose was 27 (21–43) mmol, the dose in 1978 was 30 (20–48) mmol, and the dose from 1979 up to this study was 26 (16–40) mmol.

**Table 1. Clinical data on lithium patients with 15 years or more on lithium, lithium patients who discontinued lithium treatment, and psychiatric control patients, matched for age and sex (mean ± SEM).**

<table>
<thead>
<tr>
<th></th>
<th>All lithium patients</th>
<th>Lithium patients who discontinued</th>
<th>Control-patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>n=142</td>
<td>n=13</td>
<td>n=13</td>
</tr>
<tr>
<td>Number of patients with UP/(BP + CP)/RE (%)</td>
<td>27/109/6</td>
<td>5/7/1</td>
<td>4/6/3</td>
</tr>
<tr>
<td>Duration of the psychiatric disorder (years)</td>
<td>19/77/4</td>
<td>38/54/8</td>
<td>31/46/23</td>
</tr>
<tr>
<td>Lithium treatment time (years)</td>
<td>32 ± 0.8</td>
<td>32 ± 2.2*</td>
<td>20 ± 4.0</td>
</tr>
<tr>
<td>Time spent in psychiatric hospital (months)</td>
<td>19 ± 0.2</td>
<td>18 ± 0.6</td>
<td>0</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>13 ± 1.7</td>
<td>6 ± 2.7**</td>
<td>8 ± 3.0</td>
</tr>
</tbody>
</table>

**Table 2. Clinical data on lithium patients with 15 years or more on lithium, lithium patients who discontinued lithium treatment, and psychiatric control patients, matched for age and sex (mean ± SEM).**

*a UP, unipolar affective disorder; BP, bipolar affective disorder; CP, cycloid psychosis; RE, remaining.

* Significant difference from control patients.

** Significant difference from all the lithium patients.
Renal function after lithium withdrawal

Table 2. Renal function in 13 lithium patients with 15 years or more on lithium when studied both on lithium and off lithium (mean 8.5 weeks) and in 13 psychiatric control patients matched for age and sex (mean ± SEM and range)

<table>
<thead>
<tr>
<th></th>
<th>Lithium patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>on lithium</td>
</tr>
<tr>
<td>GFR ml/min/1.73 m² range</td>
<td>13</td>
<td>69 ± 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39–96</td>
</tr>
<tr>
<td>Serum creatinine µmol/l range</td>
<td>12</td>
<td>103 ± 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73–161</td>
</tr>
<tr>
<td>Umax mOsm/kg H₂O range</td>
<td>12</td>
<td>645 ± 72*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>140–187</td>
</tr>
<tr>
<td>Uvol 1/24 h</td>
<td>6</td>
<td>3.8 ± 0.9</td>
</tr>
</tbody>
</table>

*P < 0.01 versus control patients.

**Glomerular filtration rate** tended to increase while **serum creatinine** tended to decrease but the changes did not reach statistical significance. There was no significant difference in GFR between the lithium patients and the controls. Five lithium patients on lithium but no control patient had reduced GFR (P < 0.05). This difference had disappeared at the end of the lithium-free interval since only two lithium patients now had reduced GFR.

**Maximum urinary concentrating capacity** did not change during the lithium-free period. The observations at 5 and 9 weeks off lithium were identical. Umax was significantly lower in the lithium patients compared to the controls. Two of the three lithium patients with reduced Umax were isosthenuric. One of them continued off lithium for 1 year but Umax did not improve. 24-h urine volume remained unchanged. However, only six patients successfully completed this test on both occasions. Polyuria was present in half of them both on and off lithium.

Routine clinical chemistry was within the normal range in all patients except for serum calcium, which was slightly increased in the lithium group off lithium compared to the control group, 2.46 ± 0.04 versus 2.31 ± 0.02 mmol/l (P < 0.01). Five patients had thyroxine substitution.

**Discussion**

There are no published lithium-withdrawal studies in patients who have been on lithium for about two decades. The patients in the present study were recruited from a background population of 142 long-term-lithium-treated patients in a random fashion and the present group appeared representative of this large group. The main findings are a clinically significant and irreversible reduction of the urinary concentrating capacity while the glomerular filtration rate is better maintained and tended to improve during the lithium-free interval.

Practically all the long-term lithium patients had reduced Umax in comparison to their individually matched control. Regardless of Umax level no improvement took place after lithium withdrawal. We found evidence of a major reduction of GFR in one of the patients and our results suggest that the reduced GFR found in long-term lithium patients [5] is only partly reversible.

The design of this study was similar to a previous study on a group of lithium patients [10] whose average lithium treatment time was 6 years but the results in the present group treated for 18 years differed in several ways, namely the absence of any improvement of Umax during the lithium-free interval, the magnitude of the irreversible reduction of Umax, and the presence of diabetes insipidus. The absence of an improvement of GFR is also noteworthy. These differences are highlighted by the fact that reduced tubular function was not a selection criterion in the present long-term study in contrast to our short-term study.

There are three other controlled lithium withdrawal studies of renal function in short-term lithium patients [11–13]. The results were similar to those in our short-term study [10], namely a partly reversible reduction of the urinary concentrating capacity. GFR was not measured.

Five long-term renal function studies have been published [14–18]. In two of them [14,15] an age-related GFR decline was found during 6–10 years, although in one [15] serum creatinine increased significantly. An increase of serum creatinine was also found by Gitlin [22]. We have previously shown [5] that about one-fifth of long-term lithium patients have reduced GFR, probably caused by somatic disease, which may explain the increase in serum creatinine found among these patients.

In two of the long-term studies [16,17] tubular function declined over a 5- or 7-year period, which is in accordance with our results. In the third study [18], no change took place during 8.5 years of follow-up, a result which may be questioned for methodological reasons. Many patients were lost to follow-up, some of them because they were unable to complete the 26-h water deprivation test used for the assessment of tubular function. Patients with reduced tubular function are therefore likely to have been systematically excluded.

It is interesting to note that the serum calcium was increased in lithium patients. This has been noted
previously and is probably due to a stimulation of the parathyroid glands, some patients even developing hyperparathyroidism [23].

Therefore, combining the findings in short- and long-term lithium patients, the evidence indicates that the irreversible damage of the tubular function increases with increasing exposure to lithium and lithium now appears to be a common cause of nephrogenic diabetes insipidus. In addition, lithium causes a partly reversible reduction of GFR. Lithium-induced uraemia is rare, however, and only a few cases have been described to date [19-22].

The irreversible reduction of the urinary concentrating capacity is not in itself life threatening but the accompanying polyuria is a problem and constitutes a permanent risk of negative water balance which may become dangerous under certain circumstances. It must be considered a serious side-effect of long-term lithium treatment, and these patients will always be in need of strict surveillance. Lithium should always be used cautiously in patients for whom no alternative is available.

Acknowledgements. The study received support from the following funds and institutions: University of Linköping, University of Lund, Bror Gadelius Minnesfond, Lundbeckfonden, O. M. Perssons dona-
tionsfond, Royal Physiographic Society in Lund, Sjobringfonden (Psychiatric Clinic, University of Lund), Söderström-Königska fonden and Upjohnfonden.

References

Received for publication 17.7.1995
Accepted in revised form: 8.11.1995