RENALE FUNCTION AND RENAL PATHOLOGY IN PATIENTS
WITH LITHIUM-INDUCED IMPAIRMENT OF RENAL
CONCENTRATING ABILITY

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Summary

Lithium-induced impairment of renal concentrating ability is regarded as a
harmless side effect of lithium treatment. This report presents investigations
of renal function and renal pathology in 13 patients with reduced renal con-
centrating ability arising during lithium treatment. The reduced concentrating
ability parallels histological damage and is a sign of lithium-induced chronic
nephropathy.

Introduction

It is well known that polyuria may develop during maintenance lithium
therapy1,2,3,4. Lithium-induced polyuria results from a vasopressin-resistant
impairment of renal concentrating ability2 and is usually considered a harmless
side effect. Recently, a case was reported in whom polyuria was associated
with damage to the cells lining the distal parts of the nephron5; furthermore
flattening of the epithelium and cystic dilatation of the distal tubules have
previously been demonstrated in lithium-intoxicated dogs6. Our group has
observed patients who developed chronic renal lesions during long-term lithium
treatment.

The aim of the present study was to investigate whether reduction of the
renal concentrating ability of patients on long-term lithium therapy is correl-
ated with these histological renal lesions7.

Materials and Methods

Patients

Investigation of renal function (glomerular filtration rate and effective renal
plasma flow), renal concentrating ability and renal pathology was carried out

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TABLE I. Clinical Data from 13 Patients with Lithium-induced Impairment of Renal Concentrating Ability

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Serum creatinine at start of Li⁺ treatment mg/100 ml</th>
<th>Duration of Li⁺ treatment years</th>
<th>Li⁺ dosage mmol/day</th>
<th>Serum lithium concentration mmol/L</th>
<th>Creatinine clearance at time of kidney biopsy or prior to autopsy ml/min</th>
<th>Kidney size at* time of kidney biopsy or autopsy cm²</th>
<th>Lithium intoxication in relation to histological examination</th>
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<td>55</td>
<td>♂</td>
<td>1.0</td>
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<td>48 - 24</td>
<td>0.7 - 0.8</td>
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<td>6</td>
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<td>1.0 - 1.2</td>
<td>100</td>
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(33-63)  (1⅓-15)

* Kidney size measured on intravenous pyelograms
† Unilaterally nephrectomised
Results

Renal function studies

In 6 patients renal function (Table II) was reduced, $^{125}$iodalumate clearance being below 50 ml/min$^8$. In the remaining 7 patients $^{125}$iodalumate clearance was within the normal range.

In all 13 patients impaired renal concentrating ability was found (Table II). The maximal urine osmolar concentration achieved was 682 mOsm/kg H$_2$O which in our laboratory is the lowest normal value in healthy living kidney donors with the same age and sex distribution and normal renal function (controls comprised 10 women and 7 men aged 37-69 years, mean 51 years).

In five of 12 patients studied (Pat. Nos. 1,2,6,7 and 13) during lithium treatment or a few weeks after cessation of treatment, urine osmolar concentrations did not reach serum osmolar concentrations during concentration tests (Table II and Figure 1). A permanent positive free water clearance was present. During the investigation an increase in serum sodium and serum osmolar concentrations was seen and a weight loss of 4-7% of initial body weight took place. Treatment with vasopressin, chlorpropamide and spironolactone did not affect serum nor urine osmolar concentrations. During treatment with a natriuretic drug (cyclopenthiazide 0.50 mg/day, orally) a decrease in serum sodium and serum osmolar concentrations and an increase in urine osmolar concentrations were seen in patients Nos. 1,2,6 and 7.

In the 5 patients studied during and after cessation of lithium treatment (Pat. Nos. 3,6,7,8 and 9) (Table II), a slight increase in renal concentrating ability was seen 6-12 months after lithium treatment had been stopped. In two patients (Pat. Nos. 7 and 8) renal function also improved. Patients Nos. 6 and 8 were studied during a further period of lithium treatment, 10 and 4 months, respectively. Lithium therapy had to be given up in these two patients because of a significant reduction in renal concentrating ability.

Histological examination

Renal biopsy specimens were obtained in 12 patients. Patient No. 2 had only one kidney and biopsy was therefore not done, but this patient died six months after renal function studies had been performed and the kidney was studied after autopsy. All histological specimens were characterised by focal fibrosis of a moderate to severe degree (Figure 1). In the fibrotic areas many totally sclerotic glomeruli were seen and severe tubular atrophy was present, often with thyroid-like areas with microcysts. In 6 of 12 biopsies, cysts covered with a low columnar or cubical epithelium were demonstrated.

Quantitative measurements revealed 5 times as many sclerotic glomeruli and twice as much fibrotic tissue in the cortex of the lithium-treated group.
Figure 1. Renal biopsy specimen from Patient No. 3, demonstrating three fibrotic areas, separated by preserved cortical tissue with a few dilated tubules (x 60)
Figure 2. Two focally fibrotic areas including several atrophic tubules with thick basement membranes. In the centre a sclerotic glomerulus is seen (x 240)

as compared with the control group. The lithium-treated group presented three times as many atrophic and unidentifiable tubular profiles as the control group (Figure 2).

Figure 3 demonstrates a significant negative correlation between the relative amount of atrophic and unidentifiable tubular profiles and maximal renal concentrating ability expressed in mOsm/kg H₂O in 11 patients (Pat. Nos. 2 and 10 excluded either because concentration test or renal biopsy were not performed).

Patients Nos. 1 and 2 died during the period of study. At autopsy the kidneys from patient No. 1 and the remaining kidney from patient No. 2 showed granulated surfaces with numerous small cysts which on the cut surface were seen to be located in the cortex. The kidneys appeared normal in size 11 x 6 x 3 cm and 13 x 6 x 3 cm, respectively. Histological examination showed changes similar to those described above.

Discussion

The lithium ion is almost exclusively eliminated by the kidneys; thus the daily dosage (8-80 mmol)¹⁰, during a steady state, has to appear in the urine, i.e. urine lithium concentrations reach at least 4-40 mmol/l if polyuria has not developed; these are toxic concentrations, if also present within the cells lining the distal tubules or collecting ducts¹¹.
Figure 3. The relationship between the maximal renal concentrating ability (mOsm/kg H₂O) and unidentifiable and atrophic tubule profiles in per cent of normal. Statistical method: Spearman's Rho test.

The present study included 13 patients in whom impaired renal concentrating ability was found during lithium treatment. This reduction in renal concentrating ability was correlated with the degree of tubular damage. In six patients especially investigated for reduced renal concentrating ability, this was still present 6-12 months after cessation of lithium therapy. Two patients were studied for longer periods of time and it could be demonstrated that renal concentrating ability increased slightly when lithium was not given and decreased after resuming lithium therapy. These studies demonstrate that lithium-induced impairment of renal concentrating ability is caused by damage to the tubules, a condition which was not reversible in the six cases investigated.

In six cases renal insufficiency was seen and in 11 patients the daily dosage had to be reduced, because of a reduction of renal lithium excreting ability. This condition was associated with chronic tissue damage consisting of focal fibrosis with nephronic atrophy, sclerotic glomeruli and cysts in the kidneys.

In conclusion

This study demonstrates that lithium-induced impairment of renal concentrat-
ing ability parallels histological damage to the tubules and may be associated with reduction in renal function caused by irreversible organic damage to the kidneys. Thus a lithium-induced reduction of renal concentrating ability should not be regarded as a harmless condition but rather as a sign of a lithium-induced, chronic nephropathy.

Acknowledgment

This work was supported by the Danish Medical Research Council.

References

9. Hansen, HE and Amdisen, A (To be published)

Open Discussion

MASSRY (Los Angeles) In most cases of chronic renal failure or impaired function one does not get really hypotonic urine, usually the urine is isotonic. There is ample data indicating that there is a decreased responsiveness of the renal tubule to antidiuretic hormone in lithium intoxication, so it is difficult for me to accept impaired renal function as a cause for the polyuria and ignore the issue of antidiuretic hormone. The major difficulty really lies in the lack of responsiveness of the renal tubule to the hormone rather than real renal failure. One last comment, since you are talking about renal function with lithium toxicity; lithium causes hypocalciuria and it has now been suggested for the treatment of renal stones.

HANSEN I have tried antidiuretic hormone in these patients, but I have never seen any effect of antidiuretic hormone given to these patients. The patients produce hypotonic urine until they reach a plasma osmolal level of about 360 mOsm/kg H₂O. At that point the patient is dehydrated with severe renal insufficiency.

BRUNNER (Basel) I think this is a very important study and it implies that we should be very careful - or the psychiatrists should be very careful - about putting patients on lithium. Apparently it is a very good drug for psychiatric
disorders so should we not be careful in stating that this is dangerous for the kidney? I got the impression that most of your patients were in a severely dehydrated state, judging from the osmolalities before the concentrating test. Should it not be said that if a patient develops polyuria that patient should not be treated with lithium, but all the other patients who do not develop polyuria can safely be left on lithium for years? I don’t know.

HANSEN It is not possible to answer this question, because the aim of the present study was first to investigate patients with lithium-induced polyuria and impaired renal concentrating ability. As you saw on the slides, there were five patients with claims of polyuria and urine volumes of about 2.5 to 3L per day with normal renal concentrating ability and the same results of function tests as healthy kidney donors, after several years of lithium treatment. I don’t think this group is at risk, but the patients with impaired renal concentrating ability did not normalise their renal function even if they were rehydrated. It was sometimes extremely difficult to keep these patients in positive fluid balance. Even after the serum sodium and osmolal concentration became normal their renal function was still impaired.

BRUNNER But do you suggest that the patients who do not develop polyuria and dehydration measured by elevated serum sodium are not at risk to develop this kind of renal failure?

HANSEN I don’t know, because I have not performed biopsy in these patients.

TALLQVIST (Helsinki) Do you have any idea about the mechanism of this lesion? The pictures of the changes you showed are rather like those you see in vascular lesions of the kidneys.

HANSEN No, there are no vascular lesions in the kidneys. The arteries in the kidneys did not differ significantly from age and sex-matched controls.