

LITHIUM AND RENAL FUNCTIONS

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SUMMARY

Thirty patients of affective disorder who were on lithium for a year and thirty patients on antidepressant were studied in detail for renal functions. Our observation is that lithium therapy does not lead to any deterioration in kidney functions. The results are discussed.

Since the discovery by Cade (1949), lithium has gained more and more popularity as a therapeutic and prophylactic agent for affective disorder. Of late, attention has been drawn towards its various side effects during long term therapy, especially those which affect the kidneys. Lithium is totally eliminated through the kidneys and is concentrated in renal medulla hence there is a high risk for the occurrence of renal pathology. Amongst the various renal effects of lithium, some are known to be reversible, while others are speculated to be irreversible. Amongst the reversible changes are natriuresis (Cox and Singer 1981), impaired urinary acidification (Cox and Singer 1981), and polyuria and polydipsia mediated by several mechanisms of which unresponsiveness of renal tubules to central ADH seems to be an important one (Jackson et al. 1980). The latter effect, however, is reported to be persistent and irreversible by some investigators (Robin et al. 1979, Bucht and Wahlin 1980). This impairment has also been reported due to other psychotropic agents (Wahlin et al. 1980) as well as due to the illness itself (Miller et al. 1970).

Histopathological studies have demonstrated a marked damage to distal convoluted tubules (Patfield 1975), interstitial fi-

brosis and interstitial nephritis (Hestbech et al. 1977, Burrows et al. 1978, Rafaelson et al. 1978) and necrosis of distal nephrons (Burrows et al. 1978). Hestbech and associates (1977) also reported impaired renal concentrating ability and a rise in serum creatinine. Later on controlled studies did not reveal any significant difference between lithium treated and non-lithium treated patients of affective disorders as regards renal functions (Hullin et al. 1979, Coppen et al. 1980). Contrary findings have been reported by Albrecht and associates (1980). Hence the subject of lithium induced renal changes is still controversial and reports are far from conclusive. The present controlled study aims to clarify this issue by studying the possible association between lithium therapy and renal damage.

Material and Methods

Sample:

The sample was chosen from patients attending lithium clinic of the department of Psychiatry, K. G's. Medical College, Lucknow. It consisted of two groups of patients. Group-I consisted of patients satisfying the following inclusion criteria:

1. Scientist, Central Drug Research Institute, Lucknow.
2. Lecturer, Department of Psychiatry, K. G's. Medical College, Lucknow.
3. Director, Sanjay Gandhi Post-graduate Institute of Medical Sciences, Lucknow.

- a). Age between 17-60 years, any sex
- b). Diagnosed as MDP unipolar or bipolar, currently euthymic according to ICD-9 criteria.
- c). No h/o renal disease.
- d). On regular lithium therapy for not more than one year and at least for two months.
- e). If on concomitant drug administration - only neuroleptics or antidepressants.

Group - II consisted of age and sex matched patients satisfying criteria a, b, and c as above, having no history of treatment with lithium, though receiving either neuroleptics or antidepressants for 2 to 6 months.

Procedure:

All the included patients were subjected to a detailed mental status examination and their psychiatric history was recorded. A thorough general and systematic examination was done in each case. Various socio demographic variables were recorded and each patient was subjected to following investigations:

- 1) Weight charting.
- 2) Serum lithium estimation and recording of lithium dosage.
- 3) 24 hour urine output.
- 4) Specific gravity after 12 hours fasting.
- 5) Urinary pH (using pH meter).
- 6) Urinary proteins, and urinary creatinine (Alkaline picrate method).
- 7) Urine sugar (Benedict's test).
- 8) Microscopic examination of urine.
- 9) Urinary ADH (antidiuretic hormone) (Method of Noble et al. 1950).
- 11) Serum electrolytes Na^+ , K^+ , Li^+

and Cl^- (using flame photometer, mercuric nitrate method).

12) Serum uric acid (phosphotungstic acid method).

13) Serum creatinine (colorimetric method) and creatinine clearance test (as an index for glomerular filtration rate).

Standardisation of all the biochemical investigations was done at our laboratory and the Central Drug Research Institute, Lucknow.

Results

Experimental group consisted of 30 patients of affective disorder, 4 patients were of MDP unipolar and 26 had MDP bipolar. Control group (Group C) consisted of total 25 patients, 4 of MDP unipolar and 21 MDP bipolar. There were 3 females each in both the groups, 27 males in experimental group and 22 males in control group. There was no significant difference between the two groups either in terms of age distribution or religion. Amongst the experimental group 16 patients had received lithium for 2 to 6 months (Group A) and 14 patients had received lithium for 6 months to one year (Group B).

Amongst the two groups having polyuria (defined as 24 hours urine output more than 3 litres), there was no significant difference between the experimental and control group although 3 patients in each group A and C had polyuria. There was no significant difference between the two groups in percentage of patients having impaired urinary concentrating ability as tested by 12 hours dehydration test.

The two groups of experimental patients did not have significantly different levels of urinary lithium, sodium, potassium and chloride ions. Patients having re-

Table 1
Urinary Values

	Mean \pm S. D.	Range
(a) Urinary Potassium (in Meq/Day, Normal = 25 - 125 Meq/Day)		
Group A	28.11 \pm 15.61	2.1 - 127.6
Group B	34.91 \pm 12.25	19.88 - 121.1
Group C	66.53 \pm 18.7	36.8 - 90.0
A Vs B	$t_1 = 0.96$; d.f. = 28; N. S.	
A Vs C	$t_2 = 2.97$; d.f. = 39; $P < 0.01$	
(b) Urinary Chloride (in Meq/Day)		
Group A	74.12 \pm 19.1.	76 - 230
Group B	82.63 \pm 38.5	49.3 - 251.25
Group C	156.94 \pm 47.7	39 - 113
A Vs B	$t_1 = 1.52$; d.f. = 28; N. S.	
A Vs C	$t_2 = 2.10$; d.f. = 39; $P < 0.05$	

(There were no differences between the groups as regards urine volume, specific gravity, urinary lithium, urinary sodium, urine creatinine, urine ADH and PH)

Table 2
Serum Values

	Mean \pm S. D.	Range
Serum Uric acid (Normal 3-7 mg/100 ml)		
Group A	4.57 \pm 0.71	3.3 - 5.8
Group B	4.54 \pm 0.89	3.25 - 6.2
Group C	5.4 \pm 0.58	4.0 - 6.2
A Vs B	$t_1 = 0.09$; d. f. = 28; N. S.	
A Vs C	$t_2 = 3.91$; d. f. = 39; $P < 0.001$	

ceived lithium had significantly lower level of urinary potassium ($p < .01$) and urinary chloride ions ($p < 0.05$) as compared to controls, but the values of all the patients were within normal range of variation (Table 1). There was no significant difference in the urinary creatinine and ADH levels between the experimental and control groups.

The experimental and control group did not differ from each other in terms of urine pH.

Mean serum lithium of the patients taking lithium for 2 to 6 months was 0.53 mEq/L and that of the patients taking lithium for 6 months to one year was 0.56 mEq/L. There was no significant differ-

ence between the two groups. There was no significant difference in levels of serum electrolytes (Na^+ , K^+ and Cl^-) creatinine and uric acid between the two groups of experimental patients amongst themselves and between experimental and control groups.

Glomerular filtration rate as inferred by creatinine clearance test was not significantly different between the two groups.

Discussion

This is a controlled study of 30 patients of affective disorder, who had been on lithium for a period ranging between 2 months to one year, and 25 patients of affective disorder who had not received lithium.

Measurement of total 24 hour urine volume reveals that almost equal number of patients with lithium and without lithium had polyuria (volume exceeding 3 litres), thus our study does not indicate that polyuria is a side-effect of lithium administration.

Gelenberg (1980) suggested that specific gravity measurement can be used to measure renal concentrating ability. Various methods like 12 hours dehydration test, 3-4 hours dehydration test with DDAVP, 26 hours dehydration test etc. have been used by different workers. In the present study, specific gravity of 1016 or less was taken as the measure of impaired concentrating ability. Only one patient each in the 2 - 6 months group, as well as in the control (non-lithium treated) group showed impairment in concentrating ability, a finding in conformity with that of Coppen et al. (1980), Vestergaard and Amdisen (1981) that lithium does not have effect on renal functions. Animal studies have reported a decreased ability to lower urinary pH in response to acid loading (Roscoe et al. 1976, Nascimento et al. 1977). There have been similar but inconsistent reports in experiments on human subjects (Miller et al. 1970). Our study does not support these previous observations and conforms to the observations of Venkoba Rao and associates (1979).

None of the patients presented with metabolic acidosis as is evidenced by normal serum and urinary electrolytes levels. Patients on lithium therapy had significantly lower urinary potassium and chloride as compared to patients without lithium, but the values of all the patients were within normal range of variation. The significance of this difference is therefore not much. This variation could have been due to difference in dietary intake.

Serum creatinine has been shown to be increased in patients on lithium (Vester-

gaard et al. 1979, Hansen et al. 1979). In the present study patients on lithium for 2 to 6 months had the same levels of GFR (as evidenced by serum creatinine and creatinine clearance) as those of patients on lithium for 6 months to 1 year and patients without lithium. Hullin and associates (1979) and Coppen et al. (1980) also observed similar results. Other uncontrolled studies (Venkoba Rao et al. 1979, Grof et al. 1980, Albrecht et al. 1980) have also observed normal GFR in lithium treated patients. Pre existing renal disease and mechanical and procedural difference, vitiate the results of several uncontrolled studies in this regard. Serial estimations may be the answer to this issue. Vestergaard and Amdisen (1981) in a followup study of 237 patients in long term treatment observed that neither the patients who continued nor the patients who had discontinued lithium showed any deterioration of glomerular filtration rate as assessed through determination of the 24 hour creatine clearance and the serum creatinine concentration. Apart from mechanical errors, such differences could be due to concomitant neuroleptic or antidepressant therapy (Bucht and Wahlin 1979) or due to the affective illness itself (Coppen et al. 1974).

Lithium induced defect in kidney's response to ADH has been postulated to account for nephrogenic diabetes insipidus causing polyuria (Cox and Singer 1981, Jackson et al. 1980), while a control diabetes insipidus due to long term lithium therapy has also been proposed (Cox and Singer 1981). In the present study patients neither had polyuria, nor patients had significantly different urine ADH levels.

Thus in the present study patients on lithium therapy upto 1 year did not have any deterioration in kidney functions. It should be realised however that we have studied patients who had received lithium only upto one year. What happens to patients

who receive lithium for a much longer period still needs to be studied.

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