

## **RENAL FUNCTION TESTS IN LITHIUM TREATED PATIENTS – A CONTROLLED STUDY**

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### **SUMMARY**

Results of renal function tests done on 36 patients on prophylactic lithium treatment are compared with those of 28 age matched individuals, also being treated for affective disorders but exposed only to neuroleptics and/or tricyclic antidepressants. 25% of the lithium treated patients had A.D.H. resistant concentration dysfunction resulting in polyuria and polydypsia. Serum lithium levels had a significant positive correlation with the daily urine volume and a significant negative correlation with the 12 hour urine specific gravity. No relationship was found between the total amount of lithium consumed or the duration of lithium treatment and the urine volume. Though a higher proportion of the lithium treated patients had proteinuria, it was only of a mild degree. Glomerular Filtration Rate and renal tubular hydrogen ion excretion were normal in both the test and control groups.

### **Introduction**

Lithium therapy is widely used in the treatment and prophylaxis of recurrent affective illness (Coppen et al. 1971). Lithium is eliminated from the body by the kidneys and is concentrated in the renal medulla (Cox & Singer 1981), circumstances that are favourable to the occurrence of drug induced renal disease. A number of nephro-toxic effects like natriuresis (Saran & Russel 1976), hypokalaemia (Angrist et al. 1970), renal tubular acidosis (Cox and Singer 1981), polyuria which does not respond to antidiuretic hormone (A.D.H.) (Angrist et al. 1976; Cox & Singer, 1975 & 1981), low glomerular filtration rate (Hestbech et al, 1977; Vestergahrd et al. 1979), proteinuria (Moskovitz et al 1981) and morphological changes like glomerular sclerosis and interstitial fibrosis (Hestbech et al. 1977; Venkoba Rao, 1981) have been reported in patients on lithium treatment.

On the other hand, Kinacaid – Smith et al. (1979) have found as many lesions in a control group of people with similar psychiatric disorders who have received a multitude of psychotropic drugs other than lithium as in patients who received lithium as well as psychotropic drugs and hence the psychotropic drugs were held responsible for the renal lesions. A comparative study by Hullin et al. (1979) between lithium treated and control patients (on psychotropic drugs other than lithium) failed to reveal any significant renal impairment in the lithium group.

The aim of the present study was to compare a group of patients with affective disorders who had never received lithium with patients treated with lithium and psychotropic drugs in such a way that the psychotropic drugs (other than lithium) would not affect the comparative findings.

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### Material and Methods

Sixtyfour consenting patients with manic depressive psychoses (diagnosed on the guidelines of ICD 9 - 1977) belonging to both sexes and between 22 and 55 years of age, attending the lithium clinic at Christian Medical College & Hospital, Vellore, were included in the study. All possible causes of renal dysfunction were excluded and those with diabetes mellitus, hypertension, autoimmune diseases or known renal diseases were excluded from the study. In all these patients, physical examination, serum creatinine, blood urea, qualitative test of urine for albumin, sugar and the microscopical examination were done prior to starting them on medication and were found to be within the normal limits. Medical and psychiatric charts were reviewed to note lithium toxic episodes if any, and to record the serum lithium levels, the duration and the total amount of lithium consumed.

The test group consisted of 36 patients on prophylactic lithium carbonate treatment for a period of  $25.6 \pm 23.1$  months, who were also exposed to neuroleptics, and/or tricyclic antidepressants prior to the commencement of lithium therapy and also along with lithium in the initial phase of lithium treatment. The control group was 28 age matched patients who never had received lithium but were taking neuroleptics and/or tricyclic antidepressants for a minimum period of 6 months. Variation in the duration of treatment in the experimental and control groups were unavoidable because lithium was introduced as a prophylactic treatment only in those with frequent recurrences of mania and/or depression while the control group consisted of those with first or infrequent episode of mania or depression, where relatively short term treatment with neuroleptics or antidepressants was sufficient to control an index episode. At the

time of this study, none of these patients were acutely ill and were cooperative for the procedures.

Renal function tests done were as follows:

1. Twentyfour hour urine volume.  
Patients were given verbal and written instructions about collecting 24 hour urine specimen.
2. Twelve hour fluid deprivation test.  
Specific gravity of urine was tested by the hydrometer method, after fluid deprivation for 12 hours.
3. Vasopression (A.D.H.) Test.  
Whenever the 12 hour fluid deprivation test showed a specific gravity of less than 1020, the tubules' ability to concentrate was tested by giving Inj. Vasopression Tannate in oil, intramuscularly, after the urine was voided completely. Urine was collected for the next 4 hours and the specific gravity was measured.
4. Twentyfour hour urinary protein excretion.  
Values above 150 mg. were considered significant.
5. Tests of Glomerulter Filtration Rate
  - i) Serum creatinine - value above 1.4 mg% was considered abnormal.
  - ii) The classical creatinine clearance, which requires 24 hour urine collections, was corrected for body surface area and compared with the reported average 24 hour creatinine clearance values of 84 ml/min. in normal Indian subjects (Shah & Trivedi 1974).
  - iii) Ideal creatinine clearance, calculated by the method of Cockcroft and Gault (1976), which is based on age, weight and serum creatinine. This was compared with the classical creatinine clearance, so that it would minimise the error from improper urine collection. It was con-

sidered that a patient has low GFR, if the classical as well as the calculated Cockcroft creatinine clearance values were on or below the fifth percentile of the normal value.

Other tests used to assess renal functions were estimation of (6) Urine pH (7) Plasma bicarbonate (8) Serum sodium and potassium (9) Qualitative examination of urine for albumin and sugar and (10) Microscopic examination of the centrifuged urine sediment.

Current serum lithium levels were estimated by the flame photometry method. All patients were specifically enquired for the presence or absence of excessive thirst and passing large volume of urine.

### Results

The mean urine volume of the lithium treated patients was significantly higher and the mean specific gravity was lower than the control group. Nine (25%) out of the 11 polyuric (more than 3000 ml/day) patients in the lithium treated group had vasopressin resistant concentration dysfunction (Table). Twenty subjects of the test group had urine specific gravity of less than 1020, of which 14 of them showed resistance to the vasopressin test. One among the latter had a high serum sodium level (150 mEq/L). The 24 hour urine protein excretion ranged from 37 to 219 mg. in the control and 50 to 420 mg. in the test group.

All those who have complained of excessive thirst and passing large volumes of urine had polyuria.

The creatinine clearance values, measured by the Classical and Cockcroft methods did not differ significantly in either of the groups (Control group-paired  $t = 1.99$  N.S. ; test group-paired  $t = 1.59$  N.S.). None of the patients had a GFR

measured by the Classical as well as the Cockcroft method, on or below the fifth percentile of the normal value (84 ml/min). None of the patients had a serum creatinine level above the normal range. Urine pH and plasma bicarbonate levels were within normal limits in all these subjects.

The routine qualitative assessment of urine for albumin and sugar and the microscopical examination of the centrifuged urinary sediments were within the normal limits.

The serum lithium levels ranged from 0.5 to 1.4 mEq/L (Mean  $\pm$  S.D. =  $0.87 \pm 0.22$  mEq/L). None of the patients had episodes of lithium toxicity during their course of treatment. The mean amount of lithium consumption was  $809 \pm 814.87$  gms (Range 81 to 3450 Gms).

There was no significant correlation between the daily urine volume of the test group and the total amount of lithium consumed ( $r = 0.12$ ) or the duration of lithium therapy ( $r = 0.58$ ). Similarly there was no significant correlation between the 12 hour fluid deprivation specific gravity values and the total lithium consumption ( $r = 0.14$ ) or the duration of lithium therapy ( $r = 0.045$ ). However the serum lithium levels showed a significant positive correlation with the daily urine volumes ( $r = 0.739$  ;  $p = 0.001$ ) (Figure 1) and a significant negative correlation with the 12 hour specific gravity ( $r = 0.638$ ;  $p = 0.001$ ) (Figure 2).

### Discussion

The present study suggests that lithium has a polydipsic polyuric action. Twentyfive percent of the lithium treated patients had an A.D.H. resistant polyuria. The present study confirms the previous reports of an impaired concentrating

Table  
Comparison of Renal Functions of Patients with and without Lithium Therapy

Renal Function Tests	Control Group n = 28	Test Group n = 36	Differences between Control & Test Groups
24 hour Urine Volume Mean $\pm$ S.D.	1518 $\pm$ 1028.3	2525 $\pm$ 1207.8	$p < 0.001^*$
Number of cases with polyuria	1	11	$p < 0.05^*$
12 hour specific Gravity Mean $\pm$ S.D.	1025 $\pm$ 8.45	1010 $\pm$ 8.16	$p < 0.01^*$
Number of cases with vasopressin resistant concentration defect	2	14	$p < 0.01^*$
24 hour urine protein Mean $\pm$ S.D.	99 $\pm$ 47.7	160 $\pm$ 94.3	$p < 0.01^*$
Number of patients with proteinuria of 150 mg./day	5	18	$p < 0.05^*$

\* = Significant

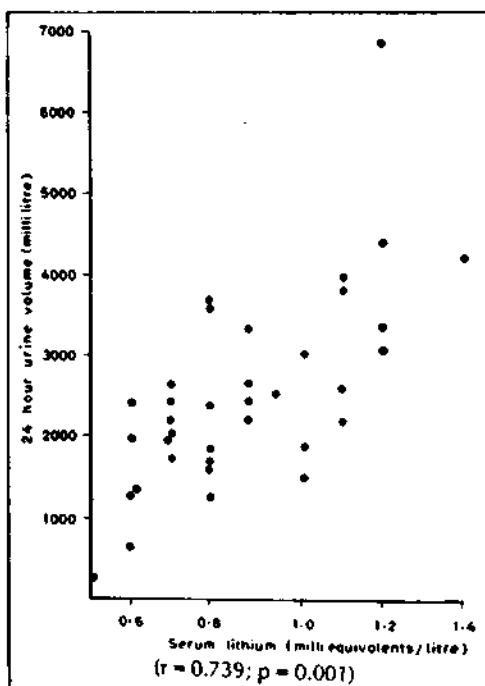


Figure 1

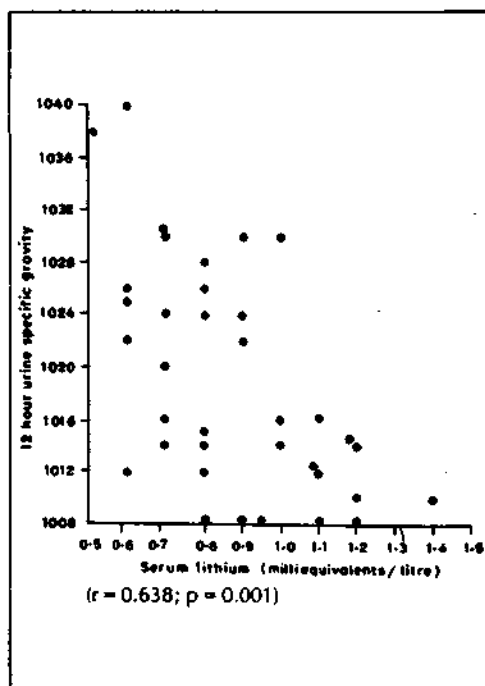


Figure 2

capacity in lithium treated patients (Bucht and Wahlin 1980; Venkoba Rao 1979).

A few patients with A.D.H. resistant concentration dysfunction did not have their daily urine volume exceeding 3 litres.

It could probably, be due to an improper collection of urine.

It is interesting to note that there is a positive correlation between the serum lithium values and the daily urine volumes

and a correspondingly negative correlation with the specific gravities.

This study could not establish any relationship between the total amount of lithium consumed or the duration of lithium treatment and the urine volume. This finding is in agreement with the earlier reports that polydipsia and polyuria are seen during the initial period of ingestion, and also appear or reappear as late side effects after months or years of lithium treatment (Shopsin & Gershon 1973).

The observation that all those lithium treated patients, who complained of excessive thirst and passing large volumes of urine had polyuria has some practical implications.

1. Such patients are likely to have a drug induced concentration defect.
2. Those complaints are clinical indicators for frequent monitoring of their renal functions.

Hypernatremia detected in one of the lithium treated patients ( $\text{Na} = 150 \text{ mEq/L}$ ) could probably have resulted from the A.D.H. resistant polyuria observed in this patient.

A higher proportion of a mild degree of proteinuria was observed in the lithium group, though none of them had gross proteinuria. Hullin and associates (1979) studied patients on long term lithium treatment and compared them with an age and sex matched group of psychiatric patients who were taking other psychotropic drugs. No significant differences in Beta-2-microglobulin excretion (an indicator of renal tubular damage) was found. In the present study, we have not employed the sophisticated tests for detecting renal tubular dysfunction. Similarly, histopathological examination was not done, as the observed abnormalities in the renal function test did not warrant an invasive procedure like renal biopsy.

The glomerular function as measured by G.F.R. has been found normal in both the groups. Recently published studies vary widely in the quantitative assessment of G.F.R. in lithium treated patients. Our observation is consistent with that of many other investigators (Gerner et al 1980, Venkoba Rao 1979, Vestergaard et al. 1979).

None of our subjects had defective renal tubular Hydrogen ion excretion as measured by the urine pH and plasma bicarbonate levels. An incomplete renal tubular acidosis has been reported among lithium treated patients (Perez et al. 1975). Viol (1975) found normal urinary acidification in all the 10 lithium treated patients he studied, in response to ammonium chloride ingestion.

There are a few limitations in the present study. First, the number of patients studied, is relatively small when compared to the previous studies and for this reason, we did not attempt to differentiate the possible minor variation between the male and female subjects. Second, this study is cross sectional in design and is lacking all the data on renal functions before the initiation of lithium therapy.

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