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RENAL FUNCTION AFTER LONG TERM TREATMENT WITH LITHIUM

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SUMMARY

Renal functions of 30 patients of manic depressive psychosis on long term lithium prophylaxis have been studied and compared with 15 age and sex matched patients receiving psychotropic drugs other than lithium. The urine output more than 2.5 L/day was seen in 12 patients (40%) while impaired capacity to show urinary osmolality more than 500 m Osm/L after overnight fluid deprivation was seen in 6 patients. Creatinine clearance ranged between 70–106 ml/min (mean 89 ml/mt). Creatinine clearance less than 70 ml/min was seen in 3 patients. The ratio of urinary and serum creatinine showed statistically significant ($p<.001$) low value in lithium treated group. There was also significant increase in mean uric acid excretion in patients on lithium therapy. It is recommended that inspite of serum lithium levels being in normal range, renal functions should be assessed regularly in order to avoid progressive impairment of renal functions.

Introduction

Lithium has been accepted as the most effective prophylactic therapy in patients with recurrent manic depressive psychosis and is commonly used (Prien et al. 1972). However during the last few years the main interest has been focussed on hazards involved in this therapy. Various studies have reported side effects of long term lithium mainly on thyroid (Villeneuve et al. 1974) and kidney (Hallgren et al. 1979, Myres et al. 1980, Vestergaard et al. 1979). Among the known side effects of Lithium on kidney functions, impaired ability to concentrate the urine during water deprivation or vasopressin resistant diabetes insipidus like syndrome (which is progressive and reversible) is most frequent (Uldall 1979). Hestbech et al. (1977) and Venkoba Rao et al. (1981) reported interstitial lesions in the renal biospy specimens of patients receiving lithium for many years. In order to avoid serious impairment of renal function lower doses of lithium are now recommended (Vestergaard et al. 1979). Although lithium is being used in many psychiatric centres in India, data regarding its long term effects are still scanty. Prompted by these reports of the drug's nephrotoxic effects, we assessed the renal function of a number of patients receiving long term lithium therapy.

Material and Methods

The present study was conducted at Department of Psychiatry of Smt. Sucheta Kriplani Hospital, New Delhi. Included

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in the study were 58 patients of affective disorder on lithium prophylaxis for more than one year (Group A). Out of these, 28 cases did not turn up for various tests and hence had to be excluded from the study (so total number of patients included in the study for final analysis were 30). Their ages varied from 26 to 55 years (mean 36.8 year). The duration of lithium therapy varied from 1 to 6 years with a mean of 2.4 years. The daily dose varied from 450–1200 mg with a mean of 900 mg. Serum lithium was estimated at least once in two months and serum lithium levels were maintained between 0.6 and 1.2 m Eq / L. The patients having irregular intake of lithium or concurrent neuroleptic medication or physical illness were excluded from the study. 15 age and sex matched patients constituted the control group and were subjected to similar tests (Group B).

Renal Function tests

Twenty four hour urinary volume: 24 hour urine samples were collected under strict supervision on two consecutive days and the mean daily urinary output was calculated. Polyuria was considered when the mean urinary output was more than 2.5 litres per day.

Urinary specific gravity and osmolality were measured after 12 hours of overnight fluid deprivation. Apparent defect in concentration was considered when specific gravity more than 1016 and osmolality more than 500 m Osm / L could not be achieved. Specific gravity was measured by a densitometer and osmolality by Flask Osmometer. Urinary pH was measured in fresh morning sample.

Blood urea was estimated by Diacetyl Monoxime method and serum sodium, potassium, lithium by Flame Photometer (Hald 1951), urinary sodium and potassium by Flame Photometer, serum and urinary creatinine by Jaffe Reaction, serum and urinary uric acid, and routine macroscopic and microscopic examination of urine was carried out in all cases.

Results

None of the patients showed any glycosuria or proteinuria. Microscopic examination of urine also did not show any abnormality in any of the cases. Blood urea and serum electrolytes were within normal range.

12 (40%) lithium treated patients showed a daily urinary output exceeding 2.5 litres (out of these, 11 patients had urine output in range of 2.7 to 4.5 L/d while one patient had urine volume 6.1 L/d. Six patients (20%) failed to concentrate urine above 500 m Osm/L after overnight fluid deprivation. After 12 hour dehydration, in group A, 12 patients had specific gravity (SG) less than 1016 and the lowest SG 1009 was observed in one patient with urine volume 6100 ml/d, his creatinine clearance was 50.07 ml/mt, serum creatinine was highest (1.47 mg%) but there was no apparent clinical sign of renal failure. None of the patients in group B had SG less than 1016. The pH of morning sample of urine varied from 5.56 to 7.12 which did not reach the level of statistical significance when compared with control group.

Serum creatinine varied between 0.7 to 1.47 mg/dl. Mean 24 hours urinary creatinine values of each group was within normal range. The range of creatinine clearance (ml/mt) of group A and B were 43.52 to 122.25 and 80.02 to 125.65 respectively. Only three patients on lithium had creatinine clearance less than 70 ml/mt. The patient having creatinine clearance

50.07 was on lithium for 1 $^1/_2$ years and had the maximum urinary output of 6100 ml/24 hours, the lowest SG and highest serum lithium levels. The patient having creatinine clearance 43.52 was 52 years old and was on lithium for 48 months, his urinary output was 3720 and specific gravity 1010. Third patient having creatinine clearance 56.08 was on lithium for 11 months and was having polyuria (urine volume 4500 ml/24 hrs.) and SG was 1012.

Serum uric acid and 24 hours urinary proteins of group A and B patients did not show any abnormality.

Discussion

In the present study, 40 per cent of the patients on lithium showed a concentration defect while 20% of these developed significant polyuria (> 3L / d). Polyuria in lithium treated group has also been reported by Cattell et al. (1978), Forrest et al. (1974), Vestergaard et al. (1979), Walker et al. (1981), Hetmar et al. (1986) in 4, 13, 30, 10 and 85 per cent of cases respectively. A number of probable explanations have been tendered to explain lithium induced polyuria. Firstly, lithium inhibits the ADH synthesis and storage at central level (Singer et al. 1972, Forrest et al. 1974). Secondly, lithium impairs the renal concentrating capacity by virtue of both ADH dependent (mediated mainly through cyclic AMP) and ADH independent mechanism (Singer and Franko 1973). Thirdly, polyuria has been described as the result of direct action of lithium on collecting ducts (Hochman and Gutman 1974). Some other studies (Khandelwal et al. 1984, Sethi et al. 1987) did not find increase in 24 hours urinary volume in lithium treated patients in comparison to control group.

The inability to concentrate urine above 500 mOsm / L, as was also reported by Hansel et al. 1979), Wahlin et al. (1980), Walker et al. (1982), Plenge et al. (1982), was found in 20 per cent cases. The striking observation in the present study was the concurrent presence of polyuria and impaired concentration ability in 50 per cent polyuric patients. Out of these, two patients did not show deficit in concentration ability on estimation of specific gravity. This may be ascribed to the urinary excretion of more molar substances like urea and certain non-reducing sugars, which may increase the specific gravity inspite of polyuria.

Mean GFR as measured by creatinine clearance did not show any significant change among the groups. However, reduced creatinine clearance (less than 90 ml / mt) was seen in 40 per cent cases in lithium group. Similarly Uldall et al. (1981), Albrecht et al. (1980) and Bendz et al. (1983) observed reduced creatinine clearance in 17, 30 and 30 per cent patients respectively. Several other workers (Uldall et al. 1980, Venkoba Rao et al. 1981, Jensen and Rickers 1984, Bendz 1985) have reported that the patients who have reduced GFR after receiving long term lithium treatment, have been shown to have interstitial nephropathy. Vestergaard et al. (1979) suggested that if lithium treatment affected glomerular function, it did so only moderately and slowly. No case of terminal renal failure due to long term lithium therapy had been reported so far.

The ratio of urinary creatinine to plasma creatinine showed relatively low value in lithium treated group ($p < 0.001$). This indirectly suggests some degree of nephron loss, thereby decreasing clearance of creatinine. Mean urinary and plasma creatinine ratio in relation to urinary sodium showed a significantly higher value in lithium group, thus suggesting loss of sizable amount of urinary sodium.

Table
Renal Function in 30 treated and 15 control patients

Test	Lithium Group (Mean ± S.D.)	Control Group (Mean ± S.D.)
Serum Na^+ (meq/L)	136.95 ± 5.29	134.33 ± 4.68
Serum K^+ (meq/L)	3.92 ± .40	3.73 ± .15
Serum uric acid (mg%)	4.78 ± 1.23	4.22 ± 1.43
Serum creatinine (mg%)	0.99 ± .19	.99 ± .13
Blood urea (mg%)	24.09 ± 6.55	20.33 ± 6.35
Urinary Sodium (meq/L)	94.24 ± 11.68	85.48 ± 7.82
Urinary Potassium (meq/L)	38.60 ± 7.14	37.82 ± 9.42
Urinary Creatinine (gm/24 hrs)	1.22 ± .57*	1.48 ± .29
Urinary Uric acid (mg/24 hrs)	498.71 ± 126.15*	366.33 ± 137.91
Urinary Proteins (mg/24 hrs)	99.52 ± 28.81	97.5 ± 26.79
Creatinine clearance (ml/mt)	88.79 ± 18.80	102.58 ± 15.09
24 hrs urinary volume (ml)	2615.24 ± 1107.95*	1966.67 ± 1132.05
Mean specific gravity	1.016 ± .0037**	1.019 ± .0014
Urinary pH	6.21 ± .465	6.14 ± .49

p valves * <0.05, ** <0.01

Mean serum and urinary sodium levels were found to be within normal range. This is also reported by Donker et al. (1979), Coppen et al. (1980), Khandelwal et al. (1983). Absence of any significant change in mean serum and urinary potassium was in accordance with Coppen et al. (1980), Sethi et al. (1987) but Zadeh and Zeller (1977) noted hypokalemia associated with cardiac arrythmias in patients with lithium toxicity. For this , they gave the explanation that lithium induced natriuresis, in turn, causes hyperaldosteronism, which was responsible for kaliuresis and ultimately hypokalemia.

As reported by Coppen et al. (1980), Waller et al. (1985), Sethi et al. (1987), there was no increase in mean serum and 24 hour urinary creatinine levels. This is in contrast to other studies (Vestergaard et al. 1979, Hansen et al. 1979), which reported increase in serum creatinine levels in patients on lithium.

Increase in mean 24 hours uric acid excretion in patients on lithium for more than one year was found to be statistically significant. The precise mechanism responsible for increased uric acid excretion was probably due to involvement of proximal tubule, thereby decreasing reabsorption of uric acid.

As reported by Coppen et al. (1980), mean urinary pH was found to be within normal limits, but Walker et al. (1982) reported impaired acidifying capacity in patients on lithium therapy. In animals, there is decreased ability to lower urinary pH in response to acid loading (Nascimento et al. 1977). This can be explained on the basis of structural change in the distal convuluted tubules leading to impaired excretion of H^+ ions or acid in the urine inspite of acid challenge of exogenous or endogenous nature.

In conclusion, we observed that even after average daily lithium dose of 900 mg and average serum lithium levels of 0.73 ± 0.16 meq/L, 40 per cent lithium treated patients developed polyuria out of which 50 per cent also showed impaired concentration ability. Reduced creatinine clearance as well as decreased ratio of urinary to plasma creatinine were also found in patients taking lithium. This is indeed impor-

tant that lithium should be given for prolonged periods only in cases where it is absolutely necessary and advantages of therapy outweigh the possible risks.

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