Indian Journal of Psychiatry, 2000, 42 (4), 410-414

LONG TERM EFFECTS OF LITHIUM ON GLOMERULAR FILTRATION RATE IN INDIAN SUBJECTS - A CROSS SECTIONAL STUDY

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ABSTRACT

Glomerular filtration rate (GFR) was evaluated in thirty patients on lithium and in thirty healthy prospective kidney donors by single compartment, multiple sample plasma clearance method using ^{99m}Technetium diethylene triamine pentaacetic acid (^{99m}TC-DTPA). Normality test revealed that dose and treatment duration were skewed and the coefficient of skewness were 0.067 ($p<0.0001$) and 1.41 ($p<0.0001$) respectively. Age was marginally skewed ($p = 0.04$) for the control group. At 5% significance level, dose and creatinine were negatively correlated ($r = -0.030$). whereas age and duration were positively correlated ($r = +0.53$) (single tailed only). Duration and GFR seems to be negatively correlated ($r = -0.23$), however this correlation did not reach statistically significance level. In the present cross sectional study, no significant difference in mean GFR was observed in lithium treated affective disorder patients when compared with the age matched normal subjects.

Key words : Lithium, affective disorder, kidney, glomerular filtration rate

The potential therapeutic uses of lithium (Li) salts were suggested in the nineteenth century, however, the immense benefit of Li in psychiatric practice has been realized since last 5 decades (Reifman & Wyatt,1980). Lithium treatment may lead to changes in various organ functions and as a part of evaluating the side effects of Li, we have reported that it causes sub-clinical hypothyroidism in a significant number of Li treated patients (Deodhar et al., 1999) and also causes alterations in the blood levels of various essential elements including sodium and potassium in humans (Singh et al.,1998) and animals (Singh et al.,1994).

Currently, it is estimated that at any one time about 1:1000 of the populations of most western societies are taking Li prophylaxis for severe bipolar and unipolar affective disorders (Davison et al.,1998). The margin between 'therapy' and 'toxicity' is so narrow that the most serious complications of lithium are acute lithium intoxication (Hansen & Amdisen,1978). As the kidneys almost exclusively excrete lithium, the development of acute Li-intoxication is usually due to decreased renal elimination of this ion. Given the wide spread use of lithium, it was alarming, but perhaps not so surprising, when the 1st report of possible lithium induced chronic histological lesions of the kidneys appeared (Hestbech et al.,1997).

Polyurea and polydypsia in-patients on chronic lithium treatment results from impaired urinary concentrating ability. The nephrogenic diabetes insipidus in these patients is because of insensitivity of the collecting ducts to exogenous and endogenous vasopressin, at the level of cellular vasopressin - sensitive adenylate cyclase activity. As the primary mode of excretion of lithium by the kidneys is reassorption from proximal tubules, recent studies have suggested lithium-induced abnormalities in proximal functions (Davison et al.,1989).

Walker et al. (1982) reported that parameterrs to evaluate glomerular filtration

function i.e. serum creatinine, ^{51}Chromium ethylene diamine tetra-acetic acid (^{51}Cr-EDTA) clearance and serum ß2-microglobulin in lithium treated patients demonstrated a significant impairment when compared with affective disorder (AD) patients not receiving the drug. Tyrer et al. (1983) also reported deterioration of glomerular filtration rate (GFR) with long-term lithium therapy. Further, Jensen and Rickers (1984) reported that after lithium therapy, a significant proportion of patients (10/13) had lower GFR when measured 2 years after lithium treatment.

However, there had been a considerable lack of information on the chronic effect of lithium treatment on renal functions in Indian population. In view of this, the present cross sectional study was carried out with an ethnic prespective and the long term effect of lithium treatment on GFR was evaluated in AD patients.

MATERIAL AND METHOD

Study subjects and treatment : Thirty AD patients receiving lithium as lithium carbonate were enrolled for the present study. Thirty age matched healthy subjects who were prospective kidney donors and who had never received lithium or any other drug on a chronic basis that could affect renal functions were included as a control group. An informed written consent was obtained from all the subjects participating in the study. All the patients met DSM-III-R criteria for AD (APA,1987). These patients had previously received or were receiving medications other than lithium (viz. antipsychotics, antidepressants, anticholinergics and sedative hypnotic). The patients' demographic details and the treatment schedule are presented in table-1.

GFR evaluation : GFR was estimated using the plasma clearance method. An intravenous injection of approximately 20 MBq of ^{99m}Technetium diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) was given to each study subject and a known quantity of radiotracer was kept as standard. Subsequently, two milliliters of venous blood was withdrawn from each patient at 60, 90, 120, 150 and 180 minutes by using disposable and heparinized needles and syringes. Heparinized blood samples were allowed to stand for 3-4h and plasma was separated. Radioactivity in the plasma samples, standard sample and wash solutions (0.5 ml each) was countered by using a well type gamma counter (Nuclear Enterprises, Edinburg, U.K.) The left over activity in the needles and syringes were also accounted for the purpose of calculating the total activity in the wash solution. Absolute GFR was estimated by single compartment, multiple plasma clearance method and expressed in ml/min which was then normalized for weight and height of the patient and expressed as ml/min/1.73 m^2 (Russel et al.,1985).

Estimation of serum Li levels : Serum Li levels were estimated by the flame photometry (Brown & Legg,1970).

Statistics : Normality test, correlation analysis and student's 't' test were performed and the results were considered statistically significant when p value was $\leq$ 0.05. For the test group, the values for various parameters were skewed whereas they were normal (non-skewed) for the control group.

RESULTS

Normality test revealed that dose and treatment duration were skewed and the coefficient of skewness were 0.067 ($p<0.0001$) and 1.41 ($p<0.0001$) respectively. Age was marginally skewed ($p=0.04$) for the control group. At 5% significance level, dose and creatinine were negatively correlated ($r = -0.030$), whereas age and duration were positively correlated ($r = +0.53$) (single tailed only). Duration and GFR seems to be negatively correlated ($r = -0.23$), however did not reach the significant level.

The mean serum Li levels in the lithium treated AD patients were 0.72±0.19 mEq/L (range 0.42-1.19 mEq/L) and were in the therapeutic range.

The mean GFR in AD patients undergoing lithium treatment and in the control group has

TABLE 1
PATIENT'S DEMOGERAPHIC DETAILS, TREATMENT SCHEDULE AND ABSOLUTE GLOMERULAR FILTRATION RATE (GFR) IN TEST AND CONTROL GROUPS

Group	Number of subjects (M : F)	Age (years)	Lithium treatment (Li-dose in mg/day)	Treatment duration (months)	Absolute GFR (mL/min)
Lithium treated	30 (20 : 10)	Mean=40.2±10.8 Median=38 (range=20-62)	Mean=895±150 Median=900 mg	Mean=86.6±66.6 Median=60	Mean=94.6±27.8 Median=90 (range=50-156)
Control	30 (16 : 14)	Mean=40.2±10.5 Median=39 (range=22-61)	Nil	Nil	Mean=98.8±19.3 Median=99 (range=77-146)

The difference in GFR amongst the test and the control groups is statistically non-significant

been calculated to be 98.8±19.3 ml/min/1.73 m^2 and 94.6±27.8 ml/min/1.73 m^2 respectively and the difference in GFR between the test and the control groups is statistically non-significant (Table 1).

TABLE 2
CORRELATION ANALYSIS AMONGST DIFFERENT VARIABLES IN THE TEST GROUP

	Age	Dose	Duration	GFR	Creatinine
Age	1.00				
Dose	-0.069	1.0			
Duration	0.53	-0.03	1.0		
GFR	-0.19	0.11	-0.23	1.0	
Creatinin	0.02	-0.29	0.07	0.10	1.0

Critical values (1-tail, 0.05) = + or -0.3064

DISCUSSION

The first indication about progressive impairment of glomerular filtration rate in patients taking lithium on chronic basis came from Hestbech et al. (1977). This observation stimulated a number of cross sectional studies inpatients taking lithium and most failed to show evidence of impaired renal function (Miller et al.,1979; Perez et al.,1975). In the present study, we had also observed similar findings of non-impaired GFR in lithium treated AD patients. In a recent report (Kallner et al.,1995) in a cohort of 207 patients receiving lithium, all the renal functions were observed to be within the reference range. Hetmar and Rafaelsen (1987) compared renal functions in 44 patients receiving lithium for an average of 8 years with that of AD patients not receiving lithium. They indicated that lithium clearance can be used as a measure of GFR and the results were not comparable with that of the AD awaiting initiation of lithium therapy. Further, they observed a significant correlation with age, sex and GFR. We have not observed any correlation between age and GFR in lithium treated patients, however treatment duration and GFR in the present study seems to be negatively correlated (r = -0.23), but was significant. Furthermore, we have not seen any correlation between GFR and Li-dosing and the similar observations had been made by Hetmar and Rafaelson (1987). Acute reduction in GFR associated with acute toxicity can result in acute renal failure secondary to acute tubular necrosis. Some patients may require temporary dialysis support and this impairment of GFR is entirely reversible. Unlike, the relationship between impaired urinary concentrating ability and duration of lithium therapy, a progressive deterioration in GFR with duration of lithium therapy and/or total lithium dose has not generally been observed in patients on stable maintenance therapy without episodes of acute lithium intoxication. A review of 1172 patients treated with lithium from 14 reported series (Boton et al.,1987) suggests that approximately 15% of those on maintenance therapy have GFR less than age-correlated 95% confidence limits. Occasional cross sectional studies, indicate that patients with impaired GFR tend to be in a group that has been taking lithium for many years. Studies in patients with shorter duration of lithium

treatment may not be able to detect a subtle progressive decline in GFR. As opposed to cross sectional studies, long term prospective studies in patients on lithium establish age related decline in GFR rather than a clear relationship between lithium exposure and GFR.

Although, concurrent use of other psychotropic medication can theoretically affect GFR and has not been excluded in our study. Such a relationship has not been confirmed in the literature. Moreover, because of the small number of patients in this study and patients being prescribed a number of other psychotropic medication for varying periods of time, it will be extremely difficult to assess their effect, if any, on the GFR.

It is thus inferred that the chronic use of lithium without any indication of lithium toxicity (serum lithium levels within physiological range) in affective disorder has no significant effect on GFR. Further in cross-sectional studies, evaluating effects of Li-treatment on renal functions, age matching amongst the Li-patients and control subjects should be necessarily considered.

ACKNOWLEDGEMENTS

The authors are thankful to the Director, Postgraduate Institute of Medical Education and Research, Chandigarh, India for funding this project as a part of Institute's Intra-mural Research Scheme. Technical help rendered by Ms. Sangam Sood, Senior technician, PGIMER Research Cadre during the entire course of this work is greatly acknowledged. Thanks are also due to Mr. R.C. Goel, Bio statistician, PGIMER, Chandigarh for applying the appropriate statistical tests to the results of the study.

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