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Renal Function in Patients on Lithium Treatment

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SUMMARY A cross-sectional study was performed on 66 lithium-treated patients to investigate a possibly changed kidney function, using [^{51}Cr]-EDTA clearance, and urinary excretions of albumin and β_2-microglobulin. Thirteen patients showed abnormal test results: seven had decreased glomerular filtration rate, four had increased albumin excretion and four had increased excretion of β_2-microglobulin. There was no correlation between length of treatment with lithium or hypothyroidism (10 patients) and impaired renal function. Four patients had already manifested signs of renal dysfunction before lithium treatment. The high prevalence of impaired renal function among our patients is unexplained but lithium could be one possible cause.

Lithium is widely used as a psychotropic agent in patients with manic-depressive disorders or recurrent endogenous depression. Polyuria is often observed during lithium treatment and regarded as the result of a harmless reversible kidney affection (Robak and Saetermo, 1975; Forrest *et al*, 1974). Attention has recently been drawn to the possible association between long-term treatment with lithium and chronic renal damage. In experimental animals epithelial degeneration of the distal as well as the proximal parts of tubules has been reported (Radomski *et al*, 1950; Evan *et al*, 1972). In 1977 Hestbech *et al* reported on chronic interstitial renal lesions in 13 patients receiving lithium treatment. This alarming report prompted us to perform a cross-sectional study of our patients on lithium treatment. We have so far investigated 66 patients, including the urinary excretion of albumin as a marker for glomerular proteinuria and of β_2-microglobulin as a marker for tubular proteinuria. The data obtained are discussed in relation to the length of time on lithium treatment, earlier episodes of lithium intoxication and a possible connection between lithium-induced hypothyroidism and renal damage.

Material and Methods

Patients: The material consisted of 66 unselected patients (18 males and 48 females, 25–73 years old, mean 49 years), under treatment and follow up by the Department of Psychiatry, University Hospital, Uppsala. The diagnoses were: bipolar affective disorder (n = 26), unipolar affective disorder (n = 34) and cycloid psychosis (n = 6). All patients had been on lithium treatment for between 2 months and 15 years. Lithium alone was administered to 33 patients, while the remainder received also tricyclic antidepressants (n = 16), or neuroleptic agents (n = 10) or both types of drug (n = 7). The patients had previously been examined at least three to four times a year for psychiatric symptoms, serum concentrations of lithium and creatinine, and the presence of albuminuria (measured qualitatively with test strip). They were also regularly (about once a year) examined for thyroid function. Ten of them were under treatment with thyroxin for hypothyroidism.

[^{51}Cr]-EDTA clearance: The tracer substance was purchased from Hoechst, West Germany. [^{51}Cr]-EDTA clearance was performed and calculated according to the single-injection technique described by Bröchner-Mortensen (1972). In our department the lower normal limit for glomerular filtration rate (GFR) as measured with [^{51}Cr]-EDTA clearance is 85

ml/min per 1.73 m^2 surface area for men aged 20 to 39 years and 77 ml/min for females of the same age. The decrease of GFR with age was calculated according to Smith (1951) and Bröchner-Mortensen *et al* (1977).

Urinary proteins: Urine specimens were collected for 24 h in plastic bags of four litre capacity containing three ml of a preservative solution (2 mol/l Tris HCl buffer, pH 8 with 0.2 per cent sodium azide). Urinary albumin was quantified with a polymer-enhanced immunonephelometric technique according to Lizana and Hellsing (1974). The upper normal limit has previously been given as 50 mg/l (Bohn, 1973), 30 mg/l (Rennie and Keen, 1967) or 20 mg/l (Weeke and Weeke, 1973). Our own normal material (unpublished) shows a mean value of 3.8 mg/l with ± 2 SD limits of 1–20 mg/l. However, with regard to earlier reports on albumin excretion (Bohn, 1973) and to the lognormal distribution of urinary albumin we consider only albumin values outside the + 3 SD region (> 50 mg/l) as clearly abnormal.

Urinary β_2-microglobulin was analysed with a radioimmunoassay (Phadebas β_2-micro test, Pharmacia Diagnostics, Uppsala, Sweden) following the manufacturer's instructions. The normal range for urinary β_2-microglobulin is up to 350 μg/l (Peterson *et al*, 1969).

Creatinine and thyrotropin: Blood samples were drawn from all patients at 9 a.m. before the injection of [^{51}Cr]-EDTA. Serum creatinine was analysed using an autoanalyzer technique (Technicon NIIb). The normal range for serum creatinine is 64–106 μmol/l. Thyrotropin (TSH) was determined by radioimmunoassay (TSH-

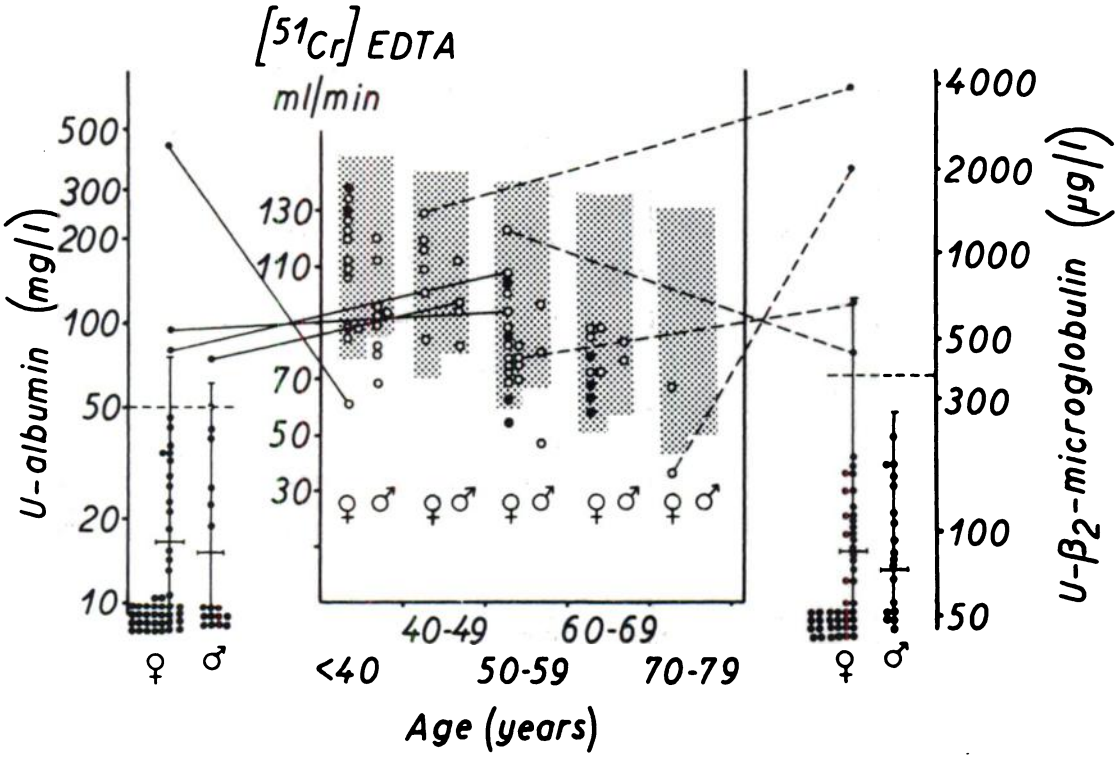

FIG 1.—Renal function and lithium: GFR in ml/min from the total [^{51}Cr]-EDTA plasma clearance in 66 lithium patients within the central rectangle: each circle represents one patient (filled circles those also receiving thyroxine). The shadowed area indicates the sex and age-dependent normal clearance values. The urinary excretions of albumin and beta$_2$-microglobulin (mean value ± 2 SD), respectively, are also illustrated. The horizontal dotted lines indicate their upper normal concentrations. Those patients with a pathological proteinuria are connected with their [^{51}Cr]-EDTA values.

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test, Pharmacia Diagnostics, Uppsala, Sweden) following the manufacturer's instructions.

Lithium analyses were performed using an atomic absorption spectrophotometer. Recommended therapeutic serum levels are 0.5–1.5 mmol/l.

Results

Figure 1 shows the [^{51}Cr]-EDTA clearance values for the patients. The decrease of clearance with age is apparent. Seven patients had impaired GFR as measured by [^{51}Cr]-EDTA clearance. The excretion of albumin and β_2-microglobulin is also shown in the figure. Four patients had urinary albumin values exceeding 50 mg/l and another four had increased excretion of β_2-microglobulin. Only one patient with pathologically increased excretion of β_2-microglobulin had impaired GFR.

The patients (n = 10) with treated hypothyroidism are also indicated in the figure. Only one of them had a clearance value below the lower normal limit and none showed abnormal proteinuria. No patient had at the time of this investigation manifest hypothyroidism (i.e. all serum TSH values were normal).

There was no correlation between the length of lithium treatment or estimated total dosage of consumed lithium, and measured variables of renal function. Three patients had had serum lithium concentrations above the recommended upper therapeutic level on one occasion, but

TABLE I

Treatment data and impaired renal function

Patients	Sex	Age (years)	Diagnosis	Li-period (years)	S-Li max (mmol/l)	Add. psych. med.	[^{51}Cr]-EDTA (ml/min)	U-Alb (mg/l)	U-β_2-μ (μg/l)
Group A									
1. HL	M	29	c	10	0.9	+ −	70	< 10	37
2. HF	M	57	u	9	0.8		49	23	156
3. NE	M	36	b	3	0.8	+	83	< 10	91
4. GH	M	39	b	8	1.4	+ −	80	40	82
5. GE	F	53	u	7	1.1		60	26	97
Group B									
6. EN	F	73	u	2	0.9	+ −	38	43	1980
Group C									
7. IL	F	37	b	2	1.0		63	427	99
Group D									
8. KO	F	55	c	13	1.1		124	46	442
9. MA	F	52	u	8	0.5		76	36	660
10. GB	F	46	u	1	0.7		129	< 10	3800
Group E									
11. GA	F	55	u	11	1.1	+	102	77	< 30
12. EP	F	50	b	15	0.8	−	84	93	72
13. AB	M	49	b	9	0.9		94	72	41
Normal values					0.5–1.5		85M, 77F	< 50	< 350

Li-period = Time on lithium therapy; S-Limax = Maximal observed serum level of lithium; Add. psych. med. + = tricyclic antidepressants, − = neuroleptic agents; u = unipolar affective disorder; b = bipolar affective disorder; c = cycloid psychosis.

Group A: reduced GFR only, B with tubular proteinuria as well, C with albuminuria as well.

Group D: tubular proteinuria only.

Group E: albuminuria only.

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none showed signs of impaired renal function. The patients were also divided into subgroups according to treatment with lithium alone or in combination with other drugs but no significant differences in proteinuria or GFR between these groups could be established.

In Table I, those 13 lithium-treated patients who had signs of impaired renal function are presented. Four of them had already documented renal dysfunction or disorder prior to the institution of lithium treatment. Patients 2 and 6 both had, at first admission to Department of Psychiatry, elevated serum creatinine values, 120 and 160 μmol/l, respectively. As judged from creatinine values GFR has not further decreased during lithium treatment. Patient 7 suffers from nephrolithiasis and her kidneys were operated on in 1967 and 1968 for renal pelvic stones. Patient 9 has had repeated attacks of pyelocystitis throughout the years.

Discussion

Measurements in urine of the amounts of high and low molecular weight (m.w.) proteins enable studies of glomerular and tubular function in kidney disease. Under normal circumstances the low m.w. protein β_2-microglobulin is freely filtered across the glomerular basement membrane in contrast to the high m.w. protein albumin. Patients with isolated glomerular lesions have an increased albumin excretion and unchanged excretion of β_2-microglobulin. Increased urinary output of β_2-microglobulin—normally reabsorbed almost completely by the proximal tubules—with unchanged or slightly increased albumin excretion suggests proximal tubular dysfunction (Peterson *et al*, 1969).

The present investigation revealed that among 66 patients, four had an increased excretion of albumin and another four had an increased excretion of β_2-microglobulin. These findings suggest early changes in renal structure and function with slight or no affection of renal filtration capacity since only two of these patients with pathological proteinuria had impaired GFR. Another five patients had slightly reduced GFR but no pathological proteinuria.

No renal biopsy was performed on our patients. However, recently Hestbech *et al* (1977) reported on 13 patients who had been treated with lithium for 1.5 to 14 years. Lesions found on light microscopy in renal specimens from these patients were unspecific, consisting of nephron atrophy and focal interstitial fibrosis. Although the same changes were seen in age-matched controls, semiquantitative assessment of renal lesions indicated among the patients a significant increase of totally sclerotic glomeruli, of tubular atrophy and amount of interstitial fibrous tissue. They also observed an inverse correlation between the creatinine clearance and the severity of renal lesions. However, it should be noted that eight of their patients were examined because of acute lithium intoxication and the other five because of severe polyuria. They found no correlation between length of treatment and severity of renal lesions. In our study we had no patient with documented severe intoxication and no patient had severe polyuria. We found no correlation between GFR, urinary excretion of albumin or β_2-microglobulin and length of lithium treatment or serum levels of lithium.

Since the prevalence of lithium-induced hypothyroidism in psychiatric patients is high (Villeneuve *et al*, 1974; Lindstedt *et al*, 1977) and since deficiency of thyroid hormones influences renal morphology and function (Katz *et al*, 1975; Salomon *et al*, 1967) we also measured the serum thyrotropin concentrations. The normal concentrations found are strong evidence against hypothyroidism. Ten patients already had thyroxine treatment but only one of them had impaired GFR, suggesting that renal dysfunction in our cases could not be attributed to present or previous thyroid dysfunction.

It has been known for many years that acute intoxication with lithium can give renal lesions (Radomski *et al*, 1950; Chapman and Lewis, 1972) but the urgent question is whether a patient with recommended therapeutic serum levels of lithium is at risk to develop chronic renal damage. At present there exists no report of chronic uraemia developing during the course of well performed lithium treatment. In our nine patients with slightly impaired renal function now and no evidence of impairment prior to starting lithium it cannot be excluded

that lithium is responsible for this dysfunction. Hestbech *et al* thought the lesions they observed could not be age dependent or arteriosclerotic. However, there is considerable evidence linking psychiatric diagnoses with excess of mortality (Ødegaard *et al*, 1952; Rorsman, 1974; Tsuang and Woolson, 1977) and recently a higher incidence of deaths caused by cardio-vascular lesions has been reported for patients with depression (Avery and Winokur, 1976). Such data may suggest that the process of ageing and of arterio-sclerosis is accelerated among patients with affective disorders, irrespective of lithium.

To clarify the role of lithium it may be necessary to perform a comparative study of renal function of patients with affective disorders without treatment, or treated with lithium, or treated with other drugs. At present we suggest that the GFR and the excretion of albumin and β_2-microglobulin should be determined before institution of lithium treatment and checked regularly thereafter. Until more data are available concerning the possible nephrotoxic effect of lithium it seems reasonable to avoid lithium in those patients who already have a reduced GFR or a pathological proteinuria.

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