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Neuroleptics, Lithium and Renal Function

DEREK G. WALLER, J GUY EDWARDS and A. POLAK

Summary: Renal function test results in 26 patients on neuroleptic treatment, who had never received lithium or antidepressants, were compared with those in a matched group, treated with lithium; also, their tubular response to DDAVP was compared with that of 25 control subjects. Measurements of serum creatinine, creatinine clearance, and urinary albumin excretion showed no abnormality attributable to either neuroleptics or lithium. The maximum urine concentrating ability after DDAVP was significantly lower in the neuroleptic group than in controls, but significantly higher than in the lithium-treated patients. There was a significant correlation between excretion of urinary β_2–microglobulin and duration of neuroleptic treatment, but mean excretion rates were the same in both treatment groups. The results suggest that neuroleptics as well as lithium impair urine concentrating ability.

While studying the effects of lithium on renal function, Vestergaard *et al* (1979) noted that patients who were receiving neuroleptics in addition to lithium had a higher urine volume than those on lithium alone. It has also been reported that patients taking the combination had a significantly lower maximum urine osmolality (Umax) in response to desamino-cys-1-8-D-arginine vasopressin (DDAVP) than those being treated with lithium on its own (Bucht & Wahlin, 1980). Other investigators have compared renal function in patients receiving lithium with that in psychiatric patients who had not received the drug. In two of these studies, there were no significant differences in the glomerular filtration rate (GFR) or Umax between lithium and non-lithium treated psychiatric patients (Hullin *et al*, 1979; Coppen *et al*, 1980), although the mean Umax was reduced in both groups. These observations suggest that psychotropic drugs other than lithium may impair renal function. In contrast, Gelenberg *et al* (1981) and Tyrer *et al* (1980) found ahigher Umax in antidepressant treated patients than in those treated with lithium.

These studies prompted us to carry out the following investigation of the effects of neuroleptics on renal function.

Method

Fifty-two out-patients (26 stabilised on neuroleptics, 26 on lithium) and a control group of 25 healthy subjects were studied. The neuroleptic group comprised 26 patients whose sex and age-distribution is shown in the Table. Of the patients, 24 were receiving depot neuroleptics, 11 being on fluphenazine decanoate, ten on flupenthixol decanoate, and three on fluspirilene, while two patients were taking pimozide by mouth. None were known to have received lithium or antidepressants; 13 had received a barbiturate or benzodiazepine at some stage of their illness, but only two patients were taking benzodiazepines at the time of the study. The patients had received neuroleptics for a total cumulative period ranging from seven months to 22 years, and all had received more than one type of neuroleptic during their illness.

The lithium group consisted of 26 patients, matched for sex and age (see Table). All patients had received neuroleptics at some stage of their illness, but only seven were taking them at the time of examination. Ten patients were receiving antidepressants, while four others had received them previously. The lithium treated patients had received total cumulative doses of lithium ranging from 22 to 5330 grammes (mean 1992 ± 286). All serum lithium estimations were between 0.4 and 1.2 mmol/l. The patients had received neuroleptics for periods ranging from ten weeks to 16 years.

The control group comprised 19 men and six women, whose ages ranged from 22–71 years (mean 41.7 ± 3.0). None had received psychotropic drugs in the past and none was on medication at the time of this examination. Only measurements of Umax were undertaken in this group.

No patients in any group had a history of urinary tract symptoms or renal disease.

All patients attended hospital for a 12-hour study period, arriving at 8.30 am after a 12-hour overnight fast. They voided urine, and a mid-stream specimen and blood sample were obtained. A four-hour urine collection was then started, the patients being encouraged to drink at least one litre of fluid in the first two hours, to achieve a urine flow greater than 2ml/min. At the end of the collection period, 2μg of DDAVP were injected intravenously. Urine was collected at one, three, five, and eight hours after the injection. The patient's weight was recorded, as were lying and standing blood pressures. Details of previous drug treatment were extracted from the case records.

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TABLE
Results

Variable	*Neuroleptic group*	*Lithium group*	*Significance/ level*
Sex: men	21	21	
women	5	5	
Age: mean (yrs)	40.5 ± 2.8	40.3 ± 2.6	NS
range	23–70	21–71	
Length of neuroleptic treatment:			
median (yrs)	5.5	4.3	NS
interquartile range	2.7–11.4	2.1–5.4	
Serum creatinine (μmol/l)	90 ± 3	87 ± 3	NS
no. $>$ or $<$ normal range	0	0	
Creatinine clearance (ml/min)	130 ± 8	112 ± 6	NS
no. > 10% below predicted	0	1	
Umax (mosmol/Kg)	799 ± 18	694 ± 38	$P<0.05$
no. < 700	3	11	
Urinary albumin excretion (μg/min)	16.4 ± 2.2	18.2 ± 4.0	NS
no. > 14.0 (refs 1, 2)	10	8	
Urinary β_2-microglobulin (μg/hr)	5.4 ± 1.4	5.9 ± 0.9	NS
no. > 15.4 (ref 3)	1	1	
Urinary NAG (μmol/min/mmol creatinine)	1.95 ± 0.48	1.38 ± 0.09	NS
no. > 1.92*	7	3	

Results are expressed as mean ± standard error
*Upper normal value established in our laboratory
†Pharmacia UK—data on file
1. Mogensen *et al*, 1979; 2. Hansen *et al*, 1981; 3. Evrin and Wibell 1972

Investigations

The following tests were carried out:

1. Serum creatinine, urea, electrolytes, calcium, phosphate, total protein, and albumin, estimated in the fasting blood sample by an SMA 12/60 multi-channel autoanalyser, and serum lithium by flame photometry.
2. Analysis of the mid-stream urine specimen for glucose and protein by dipstick (Labstix, Ames), cells and casts by microscopy, and pathogens by culture.
3. Creatinine clearance, calculated from the four-hour urine collection. The creatine clearance was also estimated . . . using the method of Cockcroft & Gault (1976) with a 15% reduction introduced for females. The same variables were used with the nomogram of Bjornsson (1979) to calculate a relative renal function i.e. how the estimated creatinine clearance related to that which would be considered normal for subjects with similar physical characteristics. By combining these estimates, an absolute value was derived for predicted creatinine clearance in subjects of similar age and weight.
4. Urine osmolality measured by depression of freezing point of the specimens collected after DDAVP injection. The results quoted are the maximum levels achieved during the eight-hour collection period.
5. Urinary albumin, estimated by immuno-diffusion (Mancini *et al*, 1965) using an aliquot of urine from the four-hour urine collection.
6. Urinary β_2 microglobulin, estimated by radio-immunoassay (Phadebas Kit, Pharmacia (GB) Ltd. Hounslow) in an aliquot of urine from the four-hour collection. Urinary pH was greater than 5.5 in all specimens examined.
7. Urinary N-acetyl-β-glucosaminidase (NAG) activity estimated by an automated fluorimetric analysis (Tucker *et al*, 1975) and the results expressed relative to the urinary creatinine concentration.

Statistical analyses

All results are expressed as mean ± standard error of the mean, or as the median and inter-quartile ranges. Correlations within the neuroleptic group were obtained from results instigated on the Minitab 80.1 statistical package (Ryan *et al*, 1981) using a Honeywell 20/80 computer running under TSS. Comparison between groups was carried out by Wilcoxon's rank sum test.

Results

No patients had postural hypotension at the time of examination, and serum electrolyte concentrations were all within the normal range.

Mid-stream urine specimen Moderate numbers of white cells (but no casts or bacterial growth) were found in specimens from two men and one women in the neuroleptic group. In the lithium group, small or moderate numbers of white cells were present in specimens from two men, and large numbers of white cells in specimens from one man and a woman who had a positive bacterial culture.

Detailed results of the following tests are listed in the table.

Serum creatinine In the neuroleptic group, there was a positive correlation between serum creatinine concentration and age ($r = 0.488$, $P<0.025$). When adjusted for age by multiple regression analysis, there was no correlation between serum creatinine and duration of neuroleptic treatment. There was no significant difference between

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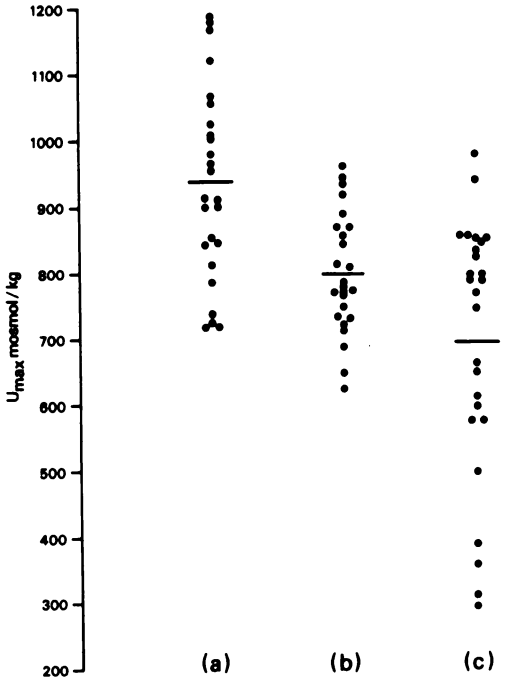


FIG. Maximum urine concentrating ability (Umax) in (a) healthy volunteers, (b) neuroleptic-treated patients, (c) lithium-treated patients. Bar indicates the mean.

the mean serum creatinine concentrations in the neuroleptic and lithium groups.

Creatinine clearance There was no correlation between creatinine clearance and age or duration of neuroleptic treatment, and no significant difference between the mean creatinine clearance in the neuroleptic and lithium groups. Creatinine clearance was lower than predicted in one neuroleptic-treated patient (measured 48 ml/min, predicted 63 ml/min). He was 70 years-old, and the four-hour urine volume was very low.

Urinary albumin excretion There was no correlation between albumin excretion and either age or duration of neuroleptic treatment, and no significant differences between the mean excretion rates for the neuroleptic and lithium groups.

Urine osmolality There was no correlation between Umax and age or duration of neuroleptic treatment. The Umax in the neuroleptic group was significantly lower than that in the control group (the mean for this group being 935 ± 29 (range 719 to 1186) mosmol/kg) and significantly higher than in the lithium group. (see Figure).

Urinary u_2-microglobulin excretion After adjustment for age, Urinary β_2 microglobulin excretion was corre lated with duration of drug treatment in the neuroleptic group ($r = 0.539$, $P < 0.05$). There was no significant difference between the two groups.

Urinary NAG Mean NAG activity was greater than normal in the neuroleptic-treated patients, but the mean excretion rate did not differ between the two groups.

Discussion

There was no evidence of reduced glomerular filtration in either the neuroleptic or lithium group. This is in keeping with the findings of Hullin *et al* (1979) and of Coppen *et al* (1980), who failed to demonstrate a difference in GFR between lithium and non-lithium treated patients. The lack of correlation between creatinine clearance and age in our patients is probably due to the very small numbers of older patients.

The mean albumin excretion rate was increased in both groups of patients, and there was no significant difference between them. However, the increase was so slight that it is difficult to determine whether glomerular leakage or impaired tubular reabsorption was responsible, and whether the drugs should be incriminated.

The Umax of all patients in the control group was greater than 700 mosmol/kg, while the mean was similar to that reported by other investigators using DDAVP (Monson & Richards, 1978b; Bucht & Wahlin, 1980). The mean osmolality in our neuroleptic treated patients was significantly lower than that in the control group and significantly higher than that in the lithium group. Our neuroleptic treated patients had not received antidepressants, and the patient groups were closely matched for duration of neuroleptic treatment. It therefore seems likely that neuroleptics alone reduce the renal concentrating ability and that lithium has additional effects.

Hullin *et al* (1979) and Coppen *et al* (1980) were unable to show a difference in Umax between lithium and non-lithium treated patients. They did not provide data on the treatment given to the non-lithium groups, but concluded that a reduced Umax during treatment of psychiatric disorders was due to factors other than lithium. These conclusions are to be contrasted with those from other studies that have shown a lower Umax in lithium treated patients than in control groups comprising patients treated with tricyclic antidepressants (Tyrer *et al*, 1980; Gelenberg *et al*, 1981). Bucht & Wahlin (1980) found a reduction in Umax in neuroleptic treated in-patients, compared with a healthy control group, but did not state whether the patients had received other psychotropic drugs. These investigators also demonstrated that patients treated with lithium alone concentrated urine less well than the neuroleptic treated group (Bucht & Wahlin, 1980).

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What is not known is the effect of the underlying illness. Psychiatric illness could reduce the intake of potassium and/or protein, which would have secondary effects on concentrating ability, and it may impair tubular function in other unspecified ways. Ellis *et al* (1970) found that random urine osmolality in pathologically depressed patients was significantly lower than in healthy controls and in other psychiatrically ill patients. Monson & Richards (1978a) and Miller *et al* (1970) demonstrated a lower mean Umax in hospitalised patients with no evidence of renal disease than in a healthy control group, but did not investigate whether this was due to illness or differences in diet and fluid intake. Following prolonged water diuresis, a solute 'washout effect' in the renal medulla may reduce concentrating ability; many illnesses may have similar effects on medullary solute concentrations (Black, 1965). Excessive water intake may be brought about by self-induced water intoxication (Smith & Clark, 1980) or be due to a dry mouth from the anticholinergic effects of psychotropic drugs. These mechanisms might affect the Umax in patients with chronic psychiatric illnesses.

Since our patients were not depressed or hospitalised at the time of the study, we conclude that the reduced Umax was caused by both lithium and neuroleptics. This supports evidence from our larger study of 101 lithium-treated patients, which suggested that the duration of neuroleptic treatment in lithium treated patients is an important factor contributing to reduced Umax (Waller *et al*, 1984), in contrast to the results of Bendz *et al* (1983), who were unable to find such a relationship.

Although there was a relationship between excretion of β_2-microglobulin and duration of neuroleptic treatment, the finding of only a single raised value suggests that there is little proximal tubular dysfunction. Lithium did not appear to have any significant additional effect in this respect. The relationship between duration of neuroleptic treatment and β_2-microglobulin excretion is consistent with the findings of Coppen *et al* (1980), who showed a higher excretion in their non-lithium group than in lithium-treated patients.

Urinary NAG excretion was increased in a greater number of patients treated with neuroleptics than in patients treated with lithium, but there was no significant difference in the means for the two groups. Other investigators have been unable to detect any increase in excretion of NAG above healthy controls when investigating non-lithium-treated psychiatric patients (Coppen *et al*, 1980; Garvey *et al*, 1982; Thysell *et al*, 1982) and urinary NAG excretion does not appear to be a good marker for distal tubular dysfunction in these patients.

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*Derek G. Waller, BSc, DM, MRCP. *Lecturer in Medicine and Clinical Pharmacology, University of Southampton, Southampton General Hospital, Southampton, SO9 4XY*

J. Guy Edwards, MB, FRCPsych. *Consultant Psychiatrist, Department of Psychiatry, Royal South Hants Hospital, Southampton, SO9 4PE*

A. Polak, MD, FRCP. *Honorary Professor of Renal Medicine, University of Southampton, St. Mary's Hospital, Portsmouth, PO3 6AD*

*Correspondence.

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