LITHIUM AND THE ANTIDIURETIC HORMONE

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- 1 The effect of lithium on the urine concentrating response to antidiuretic hormone (ADH) and the excretion of ADH has been studied in rats and man.
- 2 The maximum urine osmolarity following 18 h dehydration and Pitressin (5 u) was decreased in three out of four patients during lithium treatment compared to their response to the same test in the absence of lithium. In a fifth patient, tested only during lithium treatment, the urine remained hypotonic to plasma throughout this test.
- 3 Lithium increased the excretion of ADH in non-polyuric patients from 9-22 mu/24 h in the absence of lithium to 36-202 mu/24 h during lithium treatment.
- 4 In four patients with lithium-induced polyuria, a diuretic acting on the distal tubules, clorexolone, reduced the polyuria.
- 5 Lithium increased urine volume and the excretion of ADH in four rats receiving lithium in their diet. The response to exogenous ADH was decreased during lithium administration.

Introduction

Lithium can produce a reversible nephrogenic diabetes insipidus in rats and man (Thomsen, 1970; Singer, Rotenberg & Puschett, 1972; Forrest, Cohen, Torretti, Himmelhoch & Epstein, 1974; Harris & Jenner, 1972). This is probably due in part to the inhibition of the renal vasopressin-sensitive adenylyl cyclase (Dousa & Hechter, 1970), but there also seems to be evidence for the inhibition of the antidiuretic action of cyclic AMP (Harris & Jenner, 1972; Forrest *et al.*, 1974), and for an effect of lithium on sodium distribution in the kidney (Jenner & MacNeil, in press). Although in the alcohol-anaesthetized rat intravenous lithium has an inhibitory effect on the antidiuretic action of vasopressin within a few minutes of lithium infusion, as found by Harris & Jenner (1972), polyuria in unanaesthetized rats fed or injected with lithium develops only after 1 or 2 days. In man the polyuria does not always occur and it is not simply related to the duration of lithium treatment or to the concentration of lithium in the blood.

This paper presents attempts to look at the excretion of antidiuretic hormone (ADH) during lithium administration, and at methods of combating the polyuria induced by lithium in patients. There is also an attempt to maintain therapeutic serum lithium levels in patients in whom polyuria reduces the lithium to beneath the therapeutic range.

Methods

Human studies

Eleven patients with affective psychoses, who were receiving lithium, were studied in a metabolic ward. All medication except lithium was discontinued and patients, unless otherwise stated, had a normal diet and free access to fluids. The excretion of ADH was determined in eight of the patients during lithium therapy and in five of these the ADH was also measured when they were not receiving lithium. Renal concentration tests before and during lithium treatment were performed on five patients and on two control subjects. Three patients who developed marked polyuria were treated with clorexolone (a thiazide-like diuretic). Amiloride or Slow K was also given. Two of these patients were also given a vasopressin analogue DDAVP (1-deamino-8-D-arginine vasopressin).

Bioassay of ADH

Twenty-four hour urine samples were concentrated by ultrafiltration through selective molecular weight membranes (Oyama, Kagan & Glick, 1971) and labelled vasopressin was added for the measurement of percentage recovery. Each bioassay was on 4-6 animals. The alcohol-anaesthetized water-loaded rat preparation described by Bisset (1962) was used. The antidiuretic substance was assumed to be the

antidiuretic hormone if it satisfied three criteria: (1) the antidiuretic activity was 95% destroyed by incubation with thioglycollate (Ames & Van Dyke, 1951); (2) the substance did not affect blood pressure; (3) the antidiuretic action had a similar time course to the action of Pitressin (Parke-Davis & Co.) in the same preparation.

Renal concentrating test

The ability of the kidneys to concentrate urine was measured using the dehydration test described by Miller, Dalakos, Moses, Fellerman & Streeton (1970). Patients were deprived of fluid from 18.00 h. From 07.00 h to 12.00 h on the following day, hourly urine samples were collected for measurement of urine osmolarity. A blood sample was taken at 12.00 h for determination of plasma osmolarity and then Pitressin (5 u) was injected subcutaneously. A urine sample was collected 1 h after this injection. Urine and plasma osmolarities were determined in duplicate using a Mechrolab Vapour Pressure Osmometer. The maximum urine osmolarity of the urine in the 18 h of dehydration was compared to the osmolarity of the urine 1 h after Pitressin. The results obtained were compared with the data of Miller *et al.* (1970). The subjects were also used as their own controls.

Animal studies

The excretion of ADH and the response to Pitressin were determined before, during and after lithium chloride addition to the diet of rats. Four male rats (CFY, Remote Sprague Dawley) weighing 100 gm were kept in separate metabolic cages with free access to food and water. Food and fluid intake, as well as urine volume and body weight, were recorded daily. Lithium was added to the diet by mixing an equal weight of ground diet with 30, 45 or 60 mmol/l lithium chloride solution. The calculated daily lithium intake was approximately 0.9 mmol/24 h for 14 days, then 1.35 mmol/24 h for 7 days, and finally 1.8 mmol/24 h for 7 days for each animal.

Twenty-four hour urine collections were taken for ADH assays before lithium, after nine days of lithium administration and for 4 days after cessation of lithium treatment. The response to ADH was tested by intraperitoneal administration of 2 u/kg Pitressin. The maximum osmolarity of the urine collection in the 3 h following injection was compared to the urine osmolarity before injection. This test was carried out before lithium, after 15 and 25 days on lithium, and 7 days after lithium.

Results

Human renal concentrating ability

Five patients who had received lithium for periods varying from 5 days to 6 years were studied for their ability to concentrate urine. One patient SM, showed an abnormal concentrating response as defined by Miller *et al.* (1970), i.e. the maximum urine osmolarity after dehydration was hypotonic to plasma but increased more than 5% after an injection of Pitressin (5 u). (The urine still remained hypotonic to plasma even with this increase, however.) The other four patients were used as their own controls and in three of these patients, AP, NK and MM, lithium clearly decreased the maximum urine osmolarity after dehydration, in fact in patients AP and NK the subsequent injection of Pitressin (5 u) did not further concentrate the urine. It can be seen that the two patients tested before lithium and the two patients tested after lithium, despite significant changes due to lithium, still had maximum urine osmolarities within the normal range given for hospital patients by Miller *et al.*, (1970) (764.1 ± 45.2 mOsm/l.).

Comparing the results with those of Miller *et al.*, (1970), the reduction in maximum urine osmolarity following lithium and the relative lack of response to Pitressin are compatible with either nephrogenic diabetes insipidus or a partial ADH deficiency. It is to be noted that like Miller *et al.* (1970) we too find a difference between untreated controls and hospital patients. One patient, AP, showed a decrease in concentrating ability after only five days of lithium treatment. This subject had received lithium on two previous occasions but it had been discontinued because of a severe polyuria. This may explain the rapidity of the effect in this patient on this occasion. Lithium was given to the normal volunteers for five days but in them it did not cause a significant decrease in their maximum urine osmolarity (Table 1b).

When studied, two of the five patients, MM and SM, had urine volumes greater than 3 l/24 hours. The other patients had no polyuria (urine values below 2 l/24 h) but two, AP and NK, did subsequently develop polyuria.

Excretion of ADH in patients and controls receiving lithium

Seven patients with normal urine volume and serum lithium values within the therapeutic range (0.8-1.20 mmol/l) were studied. They were all found to have an increased excretion of ADH in the urine. The range of ADH excretion was from 36-202 mu/24 h during lithium treatment but only

9-22 mu/24 h without lithium (see Table 2). The amounts of ADH in the patients' urine before lithium therapy are appropriate for their urine volumes (Goodwin & Jenner, 1967) but the values when the patients received lithium are not.

The course of the increase of ADH excretion during lithium therapy in one of the patients is shown in Figure 1. After 13 days of lithium therapy the ADH had increased from

approximately 10 to 35-40 mu/24 hours. When this patient had received lithium for 53 days the ADH was still high, approximately 35 mu/24 h, but this increase in ADH was associated with a urine volume that increased from 1.6 to 2.4 l/12 hours. This patient did not develop diabetes insipidus.

In another patient, NK (Figure 2), the ADH excretion did not appear to increase above

Table 1a Effects of lithium on the renal concentrating ability of patients

Patient	Duration of lithium	Serum lithium (mmol/l)	Maximum urine osmolarity		Urine osmolarity (% change)	Plasma osmolarity before Pitressin
			In 18 h dehydration	Dehydration + Pitressin (5 u)		
AP	Before lithium	0	800	775	- 3.1	290
	Day 6 of lithium	0.80	625	545	-12.8	263
	Day 34 of lithium	1.36	390	380	- 2.5	290
NK	Day 70 of lithium	0.60	640	520	-18.7	290
	Day 77 of lithium	1.10	550	395	-28.2	269
	34 days after lithium	0	750	825	+10.0	279
NH	Before lithium	0	735	775	+ 5.4	290
	Day 22 of lithium	0.75	710	685	- 3.5	290
MM	1 year of lithium	0.60	325	395	+21.5	322
	18 days after lithium	0	675	675	0	290
SM	6 years of lithium	1.46	220	270	+22.7	301

Table 1b Effects of lithium on the renal concentrating ability of 'normal volunteers'

Subject	Duration on lithium	Serum lithium (mmol/l)	Maximum urine osmolarity		Urine osmolarity (% change)	Plasma osmolarity before Pitressin
			In 18 h dehydration	Dehydration + Pitressin (5 u)		
SMN	Before lithium	0	1065	1010	+ 5.2	290
	Day 6 of lithium	1.65	990	1030	+ 4.0	280
CM	Before lithium	0	890	1105	+24.1	290
	Day 6 of lithium	0.45	860	990	+15.1	290

Figure 1 The excretion of antidiuretic hormone during lithium treatment in patient MS. Horizontal bars represent the 24 h urine volume and the closed circles (●) represent the 24 h excretion of ADH.

Figure 2 The excretion of antidiuretic hormone in patient NK, who developed a vasopressin-resistant diabetes insipidus during lithium treatment. Horizontal bars indicate urine volume and closed circles (●) indicate the 24 h excretion of ADH. The administration of a vasopressin analogue (DDAVP, +) and a thiazide-like diuretic (clorexolone, x) is indicated by arrows.

Table 2 The effect of lithium on the excretion of antidiuretic hormone (mean $\pm$ s.e. mean for the number of days given in brackets).

Patient	Antidiuretic hormone (mu/24 h)	
	Control	Lithium
MD	15.3 $\pm$ 4.7 (3) Before lithium	119.0 $\pm$ 14.0 (3) 120-122 days on lithium
ED		90.7 $\pm$ 15.9 (3) 23-26 days on lithium
GA		202.0 $\pm$ 16.3 (3) 65-67 days on lithium
MN	22.0 (1) 20 days after lithium	36.0 (1) > 100 days on lithium
MC	20.3 $\pm$ 1.2 (3) 40 days after lithium	40.3 $\pm$ 5.1 (4) > 250 days on lithium
MS	8.8 $\pm$ 2.0 (3) Before lithium	35.9 $\pm$ 1.1 (3) 53-55 days on lithium
NK		128.9 $\pm$ 8.2 (3) 55-57 days on lithium
AP	21.6 $\pm$ 4.4 (2) Before lithium	249.8 (1) 7 days on lithium

Figure 3 The excretion of ADH during the addition of lithium to the diet of four rats. Urine volume is shown as the mean $\pm$ s.d., calculated at 1-4 day intervals. The 24 h excretion of ADH is shown for each animal as one of four symbols: $\square$, $\triangle$, $\circ$, $\bullet$, and plotted on a logarithmic scale.

20 mu/24 h from day 7 to 12 to lithium treatment. However, by day 55 of lithium treatment, the ADH excretion had risen to approximately 130 mu/24 h. Urine volume increased gradually from 1.5 to 2.5 l/24 h during lithium and then after 105 days of lithium diabetes insipidus developed. Urine volume increased to 8.5-11 l/24 h but the ADH excretion had now fallen to 37-79 mu/24 h. Another isolated study of vasopressin in one 24 h urine from another patient with lithium-induced diabetes insipidus showed that with a urine volume of approximately 10 l/24 h she was excreting only 49 mu/24 h of vasopressin. Both of these results would be consistent with the view that a polyuria develops because the kidney's response to ADH is inhibited and the hypothalamic compensation is inadequate, so that the urine volume can become even more massive when the production of ADH itself actually drops because of a fall-off of the compensating mechanisms.

Animal studies of renal concentrating ability and ADH excretion

The addition of lithium to the diet of rats also produces a polyuria but this appears to be dose-dependent (Figure 3). Before lithium treatment in the four animals studied, the excretion of ADH ranged from 0.7-3.0 mu/24 h but the samples bioassayed during lithium administration contained from 4.3 to 34.2 mu/24 h of ADH. All four animals

showed an increase in excretion of ADH. Two animals were investigated after lithium treatment and the ADH excretion in both returned to normal within 4 days. Urine volume, however, was still decreasing 8 days after discontinuing lithium. Except for the greater consistency of the development of the polyuria, analogous processes are probably involved in rats and men. This is especially true of the diminished response to Pitressin. The ability to increase urine osmolarity in response to Pitressin (2 u/kg given i.p.) was reduced after 15 days of lithium administration, compared to the prelithium response (Figure 4). After 24 days of lithium treatment, when the urine volume had again increased, the response to Pitressin was further reduced. Nine days after lithium the responses to Pitressin were all normal or greater than normal. The sensitivity of the rat kidney to ADH in the presence of lithium seems inversely related to urine volume under these conditions. Hence studies of rats are only partially appropriate models for human studies.

Attempts to alter the lithium-induced polyuria due to lithium ions

Treatment of lithium-induced polyuria is indicated because of the great inconvenience and especially the sleep disturbance. Further, failure to respond to lithium may well be produced by a too early rejection of the treatment in view of the side effects, or it may be due to the reduced plasma levels produced by polyuria. There is at least some

Figure 4 The effect of lithium on the urine concentrating response to Pitressin in four rats. Lines connect the urine osmolarity before Pitressin to the osmolarity 3 h after an i.p. injection of Pitressin (2 u/kg) in each animal, indicated by one of four symbols: $\square$, $\blacksquare$, $\circ$, $\bullet$. Before lithium, the mean response to Pitressin was an increase from 951 ± 239 to 1812 ± 121 mosm/litre. After 15 days of lithium the response was an increase from 724 ± 329 to 1295 ± 212 mosm/litre. After 25 days of lithium the response was an increase from 314 ± 110 to 797 ± 380 mosm/litres. Nine days after lithium the response to Pitressin was an increase from 1166 ± 216 to 2097 ± 370 mosm/litre.

evidence that the therapeutic response can be closely related to the lithium dose, as found by Hanna, Jenner, Pearson, Sampson & Thompson (1972). Three possible ways of influencing the polyuria were studied:

- (1) Treatment with a powerful antidiuretic analogue of vasopressin, DDAVP. This it was hoped could overcome the decreased responses to ADH.
- (2) The reduction of sodium in the diet and hence in the amount of sodium presented to the proximal tubules. This it was hypothesized should increase proximal tubular water reabsorption and so decrease urine volume.
- (3) Treatment with a diuretic, clorexolone, which should work paradoxically as in other diabetes insipidus-like states (Earley & Orloff, 1962).

The use of DDAVP (1-deamino-8-D-arginine vasopressin)

DDAVP was given to patient NK when he was passing 8.5–11 litres of urine a day. He received 20–30 μ g intranasally on two consecutive days, but this produced no discernible effect (see Figure 2). The same treatment was given to MJ on one occasion when her urine volume was 4 l/24 h and again there was no discernible effect. The same dose is very effective in reducing urine volume in diabetes insipidus of central origin (Vávra, Machová & Krejci, 1974).

Hence, neither Pitressin nor the more specifically powerful antidiuretic substance DDAVP are likely to be very suitable methods for overcoming the renal block produced by lithium.

Control of polyuria by reducing sodium intake

After her urine volume had risen to 6–9 l/24 h, patient MJ, who has received lithium 1.75 g/24 h for one year, was given a low sodium diet ($\text{Na}^+ = 4.75$ g/day). The urine volume was reduced to below 4 l/24 hours. It seems, therefore, that as in other forms of diabetes insipidus the reduction of sodium intake reduces the polyuria. Patients do not, however, lightly accept reduced freedom to eat as they wish for years on end, and there are dangers involved as reduced sodium intake will lower renal clearance of lithium (Thomsen & Schou, 1968).

The paradoxical use of diuretics to reduce urine volume

Four patients were treated with clorexolone. Figure 2 shows how in NK the urine volume was reduced within 3 days from approximately 10 to below 2 l/24 h by giving clorexolone (25 mg/24 h). Although amiloride (22 mg/24 h) was also given, hypokalaemia ($\text{K}^+ = 2.8$ mEq/l) and a high blood urea (8.5 mmol/l) developed, and this was associated with a rise in serum lithium to

2.23 mmol/l. This illustrates the effectiveness and dangers involved in using such combinations. In AP, however, the same regime has successfully controlled the mood and the polyuria without inducing marked potassium changes over the period of 4 months studied so far.

The third patient to receive clorexolone was the one who had a polyuria of 6-7 l/24 h, reduced by the low sodium diet (4.75 gm/day) to 4 l/24 hours. When clorexolone (25 mg/24 h) was given during this diet, the excretion of sodium increased on the first and second days of administration, but sodium excretion was only slightly elevated on the third day of treatment. The urine volume after 3 days was reduced to 2.5 l/24 h. In this patient, however clorexolone (25 mg/24 h) proved too effective when the dietary sodium was increased. When the patient took a normal diet for 3 days plus a slow release preparation of potassium, the fluid intake dropped abruptly and the serum lithium increased to 2.9 mmol/litre. The patient reported nausea and vomiting. These symptoms were relieved by discontinuation of lithium and clorexolone for a few days. The dangerous aspects of the combination were again revealed as well as the importance of the sodium in the diet. Patients must therefore have a regime which allows freedom to take reasonable quantities of sodium in their diet. Treatment with clorexolone (10 mg/24 h) was found to be effective plus a decrease in lithium dosage.

It was noticed that during lithium-induced polyuria two patients (NK and AP) showed greatly reduced serum lithium concentrations. With a reduction of urine volume, MJ and NK showed a rapid rise of plasma lithium. This predictable effect of washing out or retaining lithium can be used to maintain plasma lithium levels. To show whether this can effectively improve therapy, however, would require a very long follow-up study.

Discussion

In both man and rat lithium causes an increase in the excretion of ADH and a decrease in the response to exogenous ADH (Pitressin). The latter is well recognised in the literature (Thomsen, 1970; Singer *et al.*, 1972; Forrest *et al.*, 1974).

The response to endogenous ADH during dehydration was also presumably reduced in four of the five patients receiving lithium who were studied for their ability to concentrate urine. Hence, lithium inhibits the response of the kidney to ADH, and ADH secretion is increased to compensate for this.

Noble & Taylor (1953) and Thorn & Smith (1965) have shown that a constant percentage of infused ADH is excreted in the urine, irrespective of the amount of ADH present in the plasma, hence an increase in ADH in the 24 h urine probably does represent an increase in the circulating ADH and hence in the amount secreted.

However, one of the five patients studied did not show a significant decrease in renal concentrating ability after 21 days of lithium and the control subjects were also able to concentrate urine normally after five days of lithium. These subjects did not show polyuria. Similarly Forrest *et al.*, (1974) found that all of the ten polyuric patients he studied had concentrating defects, but only seven of the ten non-polyuric patients had abnormal renal concentrating ability. Viol, Grof & Diagle (1975) found no evidence of renal concentrating defects in any of the ten patients receiving lithium whom they studied. The urine volumes of their subjects were not reported.

Harris & Jenner (1972) showed that in the water-loaded alcohol-anaesthetized rat inhibition of the antidiuretic activity of vasopressin develops in ten minutes. Webb, Wood, Tisher & Robinson (1975) have shown inhibition has begun within one hour in primates. Jenner and MacNeil (*in press*) also present evidence to suggest that in acute studies in rats the inhibition only occurs if plasma lithium concentrations are rising. The inhibition is not simply dependent on plasma lithium concentration. Studies of 24 h urine volumes must, if this is true, often contain urine from periods when inhibition is occurring as well as periods when readjustments are made. For reasons which remain obscure after a period of intermittent inhibition, one seems bound to postulate that the kidney becomes more persistently resistant to ADH and at this stage 24 h urine volume increases and 24 h ADH levels rise. Geisler, Wraae & Olesen (1972) have produced evidence in animal studies that at this stage the renal adenylyl cyclase system itself has altered.

The polyuria does not respond to exogenous ADH in the form of DDAVP but clorexolone does reduce urine volume, apparently acting as it would in diabetes insipidus (Earley & Orloff, 1962). Levy, Forrest & Heninger (1973) gave chlorothiazide to a patient with lithium-induced polyuria and found that this reduced the polyuria. Each time chlorothiazide therapy was initiated, serum lithium concentration rose to more than 2 mmol/l as urine volume fell and the lithium dosage was subsequently decreased to reduce clinical signs of toxicity. In diabetes insipidus the thiazide and related diuretics decrease the reabsorption of sodium from the distal tubule.

This causes a compensatory increase in the reabsorption of sodium and water by the proximal tubule, so that there is less solute-free water presented to the distal tubules and collecting ducts. Hence, in the presence or absence of functioning ADH, less urine will be formed. A low sodium diet would therefore produce the same result or enhance the effect of the diuretics acting on sodium transport in the distal tubule (Earley & Orloff, 1962). In the treatment with diuretics of patients with lithium-induced polyuria, there are obvious dangers in either reducing sodium or water intake severely – both will cause an increase in the serum lithium concentration which could be dangerous (Macfie, 1975). The hypokalemia induced by the diuretics is also potentially dangerous. Great caution is therefore necessary in the presence of cardiovascular or renal disease.

On the other hand, if a considerable polyuria exists unnoticed then serum lithium levels may well be below the therapeutic level and this may often occur. We and Forrest *et al.* (1974) have found the polyuria to be common. It is usually only spontaneously reported when it disturbs the sleep of the patient.

Over a period of time presumably lithium would have some measurable effect on the kidney of every subject – there would be a decrease in the

response to exogenous ADH and a compensatory increase in urinary ADH, whether polyuria occurred or not. It is interesting to speculate that an elevated production and secretion of ADH occurs in a large number of individuals (and rats), and this is possibly only one of several hormone systems to be similarly affected by lithium acting on an adenylyl cyclase system. The behavioural effects of ADH in rats under certain learning situations are well studied (de Wied, 1965) and seem identical to those of lithium (Johnson & Barker, 1972). Certainly, few hormones have only one clearly defined function or effect and vasopressin and related polypeptides are known to affect cerebral function and behaviour. However, any relationship between lithium's inhibitory action in the kidney and the therapeutic effects of lithium still remains optimistic conjecture.

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