Long term lithium therapy in Malaysia

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Summary

Ten patients on long term lithium therapy (mean four years, range 1–10.5 years) were subjected to various renal, thyroid, haematological, cardiac and endocrine tests. There was impaired urinary concentrating ability in seven subjects, which was not responsive to vasopressin stimulation, suggesting a partial nephrogenic diabetes insipitus. Nine subjects had metabolic acidosis with higher urinary pH than expected suggesting presence of acidification defect in the kidney. No significant change in renal function, thyroid function, ECG or haematological parameters were detected. Our findings concur with previous reports from the West regarding the safety of lithium administration.

Key words: lithium, nephrogenic diabetes insipitus, renal acidification defect.

Introduction

Lithium has been used in the treatment of mania and in the prophylaxis of recurrent affective disorder. Its efficacy has been proven repeatedly over the last thirty years. However the administration of lithium is not without side effects. In the kidney, lithium has been implicated in causing interstitial fibrosis[1] through recent papers have not confirmed the initial reports.[2,3] Glomerular function has been intensively investigated in patients on lithium therapy and the overall consensus is that long term lithium administration has not affected the glomerulus.[4] Changes in renal tubular function have been reported. Firstly a nephrogenic diabetes like syndrome was noted to be associated with chronic lithium use.[5] This is important as loss of excessive fluids in the absence of adequate replenishment may result in dehydration and electrolyte imbalance. This could be exaggerated in tropical climates.

Secondly, lithium can cause a urinary acidification defect in animals and humans.[2,6] Case reports of lithium induced nephrotic syndrome which remits on withdrawal of lithium have been described.[4]

Although many patients with recurrent bipolar affective disorder are on lithium prophylaxis in Malaysia, there is insufficient published reports on lithium therapy on our local population. This is a study of ten Malaysians on long term lithium therapy.

Subjects and method

The subjects were patients attending the Universiti Kebangsaan Malaysia Psychiatric Clinic at Hospital Besar, Kuala Lumpur who had been on continuous lithium treatment for at least 12 months and have been reviewed regularly. They all gave informed consent to be examined and were euthymic at the time of the study.

The ten subjects studied consisted of seven women and three men, with history of recurrent manic depressive psychosis. One man also had alcohol dependence. The mean age was 44.3 years (range 31–58 years, S.D. 9.4 years) and a mean duration of treatment with lithium of four years (range 1–10.5 years, S.D. 2.8 years). The mean duration of their illness was 18.7 years (range 3–32 years). There was no history of lithium toxicity in all the ten subjects studied. None were involved in daily outdoor activity which could give rise to increased salt and water loss. The serum lithium levels at the time of study were within therapeutic range (0.3–1.3 mmol/l, mean 0.75 mmol/l).

Basic data regarding age, sex, occupation, diagnosis, duration of treatment with lithium and duration of illness were recorded. Previous investigations regarding renal function and plasma lithium levels were also recorded.

The subjects were admitted as in patients for the investigations. A full physical examination was carried out on admission. On first day blood was taken for full blood picture, renal profile, thyroid function tests and serum lithium analysis. Renal profile was determined using Technicom SMA-2 instrument, serum T4 determined by radioimmunoassay (RIA Abbot kit). Subjects showing abnormal T4 results were subjected to serum T3, T3 uptake and TSH analysis. Serum lithium levels were determined by atomic absorption spectrophotometry (IL Instrument). Supine and standing blood specimens were also collected at 6 a.m. and 10 a.m. respectively for aldosterone study. Measurement of plasma aldosterone was by radioimmunoassay (RIA Diagnostic kit- Abbot Laboratories). The blood samples were kept frozen till analysis by RIA. A 24 hour urine specimen was collected for the estimation of electrolytes (sodium, potassium, calcium and inorganic phosphate), uric acid and creatinine. Measurement was by flame emission photometer (Radiometer).

On the second day, blood gas analysis was carried out together with full urine analysis including microscopy for leucocytes and casts, qualitative test for nitrite, protein, glucose, ketones, urobilinogen, bilirubin and blood. The Hospital AVL 938 was used to measure blood gas and urine pH was measured by electrode method. Supine plasma aldosterone was taken at 6 a.m. followed by intravenous frusemide 40 mg. to stimulate aldosterone response. At 10 a.m. standing blood specimen was taken for plasma aldosterone measurement. The ECG was also recorded.

On the third day, saline suppression of aldosterone was carried out. After supine blood specimen was taken for aldosterone measurement at 6 a.m. two litres of saline was infused intravenously over the next four hours at the end of which standing blood specimens was taken at 10 a.m. for aldosterone measurement.

On the fourth day, after overnight water deprivation, urine and plasma osmolality was measured at 8 a.m. using the freezing point method. Those subjects who failed to concentrate urine of more than 850 mosm/kg were given 10 mg of vasopressin subcutaneously and hourly urine specimens were collected for analysis.

Results

Laboratory investigations: The full blood picture was normal in all except one subject who showed microcytic hypochromic anaemia. Serum T4 levels in all ten subjects were within reference range. The creatinine, urea and electrolytes were all within reference range. There were no abnormalities detected in the urine of all subjects. The 24 hour urine output of sodium was not increased suggesting the absence of significant natriuresis. There were no abnormalities in the ECG of all subjects. Blood gas analysis showed metabolic acidosis in nine subjects. There was adequate compensation as evidenced by a low pCO2 (Figure 1). The ammonium chloride loading test was not carried as the subjects were already having metabolic acidosis. None of the nine subjects had a urinary pH of less than 5.00 at the time of blood gas analysis (mean pH 6.16) suggesting an acidification defect in the kidneys.

Dynamic tests: Following overnight water deprivation, seven subjects had a persistently low urinary osmolality (<850 mosm/kg). The normal patient should after overnight water deprivation produce urine osmotic concentrations of >850 mosm/kg (850–1400 mosm/kg). Vasopressin stimulation on these seven subjects did not increase the urinary osmolality to more than 850 mosm/kg. (Figure 2). The low urinary osmolality is not related to the age of the subjects ($r=0.002$, $p>0.05$), the lithium dosage ($r=0.07$, $p>0.05$) or to the duration of treatment with lithium ($r=0.18$, $p>0.05$).

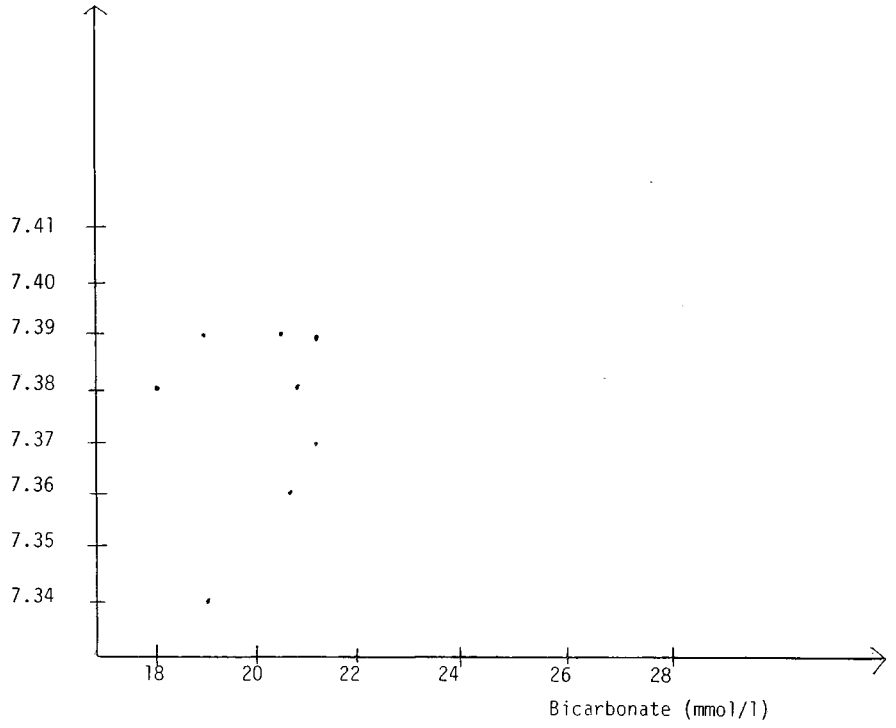

Fig. 1 Blood pH vs Bicarbonate

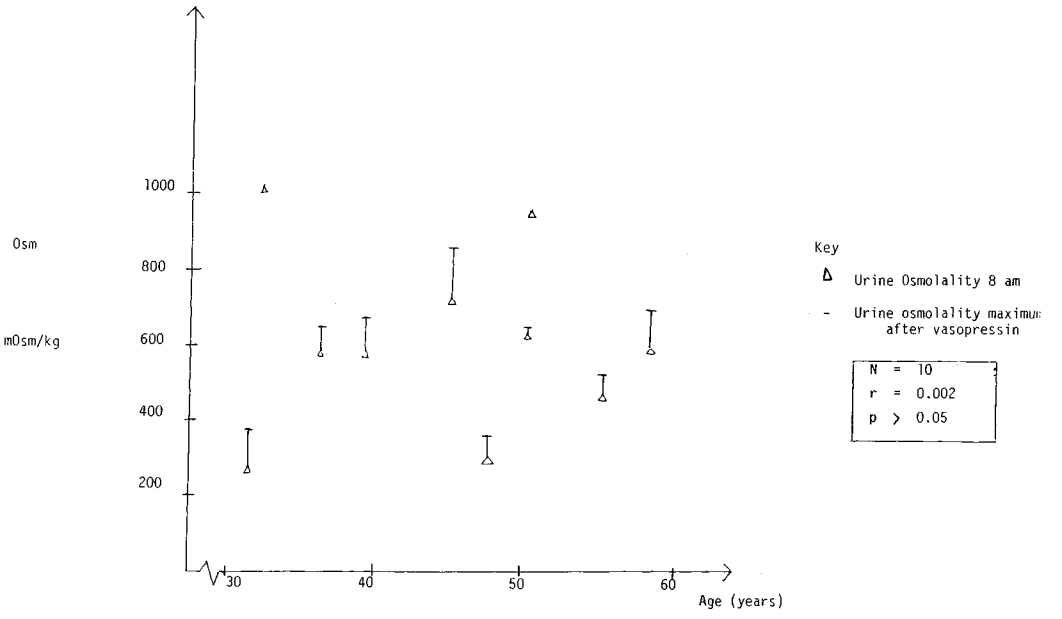

Fig. 2 Urine Osmolality Before and After Vasopressin 10 mg s/c vs Age

As the maximum urine osmolality was less than 850 mosm/kg and the urine osmolality/plasma osmolality after vasopressin was >1 the seven subjects have partial nephrogenic diabetes insipitus.

Aldosterone – response to posture, stimulation and suppression: The normal physiological response of aldosterone is increased plasma levels on standing up. With frusemide stimulation, plasma aldosterone will be further increased compared to the baseline measurements while with saline infusion the aldosterone levels will be lowered. (normal supine 6 a.m. 76–184 pg/ml, standing 10 a.m. 130–272 pg/ml). **Response to supine and erect positions**: Six subjects had a normal baseline aldosterone with normal response (increased levels) on standing. Three subjects had low basal aldosterone which also shared a normal response.

Response to frusemide stimulation: In all the subjects, plasma aldosterone was raised after frusemide stimulation. The mean increase (307.4 pg/ml) was much more than the mean increase to just standing only (129.1 pg/ml).

Response to saline suppression: Aldosterone response in all but one subject was suppressed by saline infusion despite the subject standing up suggesting that the suppressive effect of volume expansion overides the stimulating effects of posture.

Conclusions

There are two important findings from this study. First is the impairment of urinary concentrating ability that was not responsive to vasopressin in seven out of the ten subjects. They have lithium induced partial nephrogenic diabetes insipitus.

Secondly, there is metabolic acidosis with impairment of urine acidification in nine subjects. It has been reported that seven out of 15 lithium treated patients were unable to lower urine pH normally after acid loading.[6] In contrast our subjects demonstrated acidosis even without

acid loading. However, there is also a report on 10 lithium treated patients who were able to concentrate urine normally and showed normal renal tubular acidification.[7]

Although leucocytosis is commonly found in patients on lithium therapy,[8] this was not seen in any of our ten subjects.

Lithium induced goitre and hypothyroidism has been well documented.[9,10] Hypothyroidism will occur in 10–15% of females above 40 years of age and who are on lithium.[11] However none of the subjects in this study were affected and physically all were well.

Patients on lithium therapy should be well informed of the importance of maintaining adequate fluid intake and to avoid dehydration. A follow up study of blood gas analysis and urinary pH will be useful in monitoring the progress of the metabolic acidosis and urinary acidification defect. With reasonable care over fluid balance and regular monitoring, long term lithium therapy is safe, a conclusion also drawn from findings in the West.[4,12,13]

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