

LITHIUM CARBONATE IN THE TREATMENT OF MANIC DEPRESSIVE PSYCHOSIS IN CHILDREN

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SUMMARY

The authors present their experience of prophylactic lithium therapy in seven children diagnosed as manic depressive psychosis, bipolar type, according to International Classification of Diseases, 9th revision. The authors demonstrate the effectiveness of lithium as a therapeutic and prophylactic agent for manic depressive illness in children. Side-effects are not a problem if serum lithium levels are maintained between 0.6—1.2 mEq/L. Renal functions have remained un-impaired even after three years of lithium therapy in four children.

Lithium carbonate has now been well-established in the prophylaxis and treatment of bipolar as well as unipolar manic depressive psychosis in adults. Its short term side effects and long-term sequelae have also been well reported. Presence of depression and bipolar affective illness in children has been a matter of controversy for quite some time, yet many reports have appeared now describing in detail the case-histories of children suffering from bipolar affective illness (Weinberg and Brumback, 1976; Anthony and Scott, 1960; Leading article, *BMJ*, 1979; Khandelwal *et al.*, 1982; Hassanyeh and Davison, 1980). Recent studies (Hassanyeh and Davison, 1980; Brumback and Weinberg, 1977; Feinstein and Wolpert, 1973; Gram & Rafaelson, 1972) have also brought about evidences in favour of therapeutic and prophylactic use of lithium in children. So far, there have been only a few scattered reports having small number of cases. However, consensus seems to be emerging in favour of beneficial use of lithium in children as far as affective illness is concerned.

Lithium has also been tried with conflicting results in a number of other childhood disorders like hyperkinesis (Greenhill *et al.*, 1973; Whitehead and Clark, 1970), unsocialized aggressive reaction (Sheard, 1975) and childhood schizophrenia (Campbell, 1972). Despite unresolved questions such as indicators and prognosticators of lithium use, and whether to administer for an acute attack and or for prophylaxis, lithium has safely been used in children. However, information regarding its short-term and longterm side effect in children is still scanty (Youngerman and Canino, 1978). In this paper, we are reporting our experience of lithium use in seven children who developed bipolar manic depressive illness between 11-14 years of age and were then successfully treated with lithium carbonate.

SUBJECTS AND METHODS

Seven children diagnosed to be suffering from bipolar manic depressive illness are included in the study. Three were males and four females. Their ages varied between 11 to 15 years

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(mean 14 years). They all were admitted to the Psychiatry ward of the Post-graduate Institute of Medical Education and Research, Chandigarh, India for full evaluation and treatment. Cases were diagnosed according to the International Classification of Diseases 9th revision (ICD-9) which is applicable to both adults and children.

All the children had suffered variable number of attacks of mania and depression, and before the start of lithium the diagnosis of manic depressive psychosis, bipolar type had been fairly well established on the basis of history, repeated mental state examination and observation in the ward. However, in some children, some other diagnoses were also considered but requisite psychological and physical tests helped rule them out. Before starting lithium, blood haemogram, serum electrolytes and creatinine, blood urea, urinary pH and thyroid functions were carried out in each child and were found normal. Informed consent regarding lithium treatment was obtained from parents. Clinical and mental state and physical examination especially for any side effect of lithium were performed daily and recorded on a semi-structured proforma. Lithium carbonate was given in 3-4 divided doses, usually in range of 750-1200 mg/day and serum levels were determined weekly by flame photometer. Patients characteristics and important clinical features have been summarised in Table-I.

Detailed renal functions were investigated in those patients who had completed more than three years of lithium prophylaxis. For tubular function, 24-hour urine volume, and urinary osmolality were determined, and glomerular function was assessed by creatinine clearance and 24-hour urinary protein. Besides, serum electrolytes, serum creatinine and blood urea were

also measured. For the above tests, the children were hospitalized and were provided with a standard hospital diet of 2000 calories and 8 grams of salt.

RESULTS

All children had their first attack of affective illness before the age of 15 years. In three children (S. No. 1, 2, 5, 6) the illness started with depressive phase while in others (S. No. 3, 4, 7) it began with mania. All the children except case No. 4 had definite family history of affective illness. Though the diagnosis of manic depressive illness was established in all cases before the start of lithium prophylaxis, however, in the initial stages, some diagnostic difficulties had arisen in cases 1, 2, 4 and 6 as shown in the table. Treatment received prior to lithium has also been charted in the table I.

Table II summarises the age of start, daily dose, duration, serum levels, response and side-effects of lithium carbonate.

Most of the cases received 750-1000 mg of lithium carbonate daily in 3-4 divided doses with an aim of maintaining the serum lithium concentration between 0.6 to 1.2 mEq/L. Case No. 4 received 1500 mg of the drug daily for first 3 months to achieve therapeutic blood levels and then 900 mg/day subsequently, while in case No. 1, lithium dose was stepped up to 1000 mg per day after a trial of 6 months with 750 mg/day during which his blood levels stayed between 0.4-0.65 mEq/L and he continued to experience mild symptoms. In all the cases, the response to lithium therapy was visible within two weeks when the intensity of symptoms was remarkably reduced. All the cases except No. 1, became completely asymptomatic within 8-12 weeks of the treatment. Case No. 1 also became asymptomatic

TABLE 1—*Personal and Clinical History at Intake*

S.No.	Age/Sex at Contact (Years)	Age at onset of clear affective symptoms (Years)	Type of Attack at onset	Family history	Number of Depressive/manic attacks before lithium	Drugs earlier used	ECT used	Other diagnosis considered
1.	13/M	13	Depression	Maternal grandmother (Depression)	Depression —4 Mania —6	Imipramine Chlorpromazine	No	Adolescent adjustment reaction
2.	15/F	14½	Depression	Father (MDP) Uncle (Affective illness) Aunt (Affective illness)	Depression —1 Mania —1	Chlorpromazine	No	Adolescent adjustment reaction
3.	14/M	11	Mania	Mother (Epilepsy) Father (Affective illness) Uncle (Depression)	Depression —1 Mania —3	Chlorpromazine Imipramine	No	None
4.	13/M	14	Mania	Nil	Depression —2 Excitement —3	Chlorpromazine Imipramine	+ Yes	Hysteria A. C. DBS
5.	14/F	14	Depression	Grandfather (Mania) Grandfather's brother (details not known)	Depression —3 Mania —3	Imipramine Chlorpromazine	— No	None
6.	14/F	15	Depression	Father (Paranoid illness) Mother (Neurotic)	Depression —8 Mania —1	Imipramine	+ Yes	None
7.	15/F	14½	Mania	Sister (M. D. P) Grandfather (depression) Mother (Reactive Depression)	Mania —6 Depression —6	Imipramine Haloperidol	—	None

TABLE II. Summary of lithium therapy and its response

Patient	Age at start of lithium therapy (Yrs.)	Duration of lithium treatment	Daily lithium dose	Serum lithium levels (mEq/L)	Response	Side-effects	Whether lithium still continuing
1	14½	3 yrs.	750 mg for 6 months Then, 1000 mg.	0.4—0.65 with 750 mg 0.7—0.9 with 1000 mg	Complete remission	i. Tremor; ii. Frequency of micturition	Yes
2	15	4 yrs.	1000 mg.	0.7—0.9	Complete remission	Nausea	Yes
3	14	3 months	1000 mg	0.8—1.1	Termination of excitement	Vomitting	No
4	15½	5 yrs.	1500 mg. for 3 months then 900 mg.	1.0—1.3 0.6—0.8	Complete remission	Tremors	Yes
5	14	6 months	900 mg.	0.7—1.0	Termination of excitement	Nausea	No
6	17	4 yrs.	750 mg.	0.5—0.7	Complete remission	i. Nausea ii. Tremors	Yes
7	15	6 months	600 mg.	0.7—0.9	Complete remission	i. Tremors ii. Vomitting	Yes

6 months later when his daily lithium dose was increased. In view of recurrent nature of illness and significant family history of affective illness, all the cases were included in the treatment programme for a long-term lithium prophylaxis. However, two children (S. No. 3 and 5) dropped out of the treatment once they became asymptomatic. Both these cases had an attack of excitement each, one year and 6 months later, respectively, and both were again successfully treated with lithium at out-patient setting. However, they again discontinued treatment. Cases 1, 2, 4, 6 and 7 have been still on regular lithium prophylaxis and are under complete remission. Nausea, vomiting and tremors were the frequent side effects, however present only in the first 2-3 weeks of treatment. Case No. 1 also reported

increased frequency of micturition but transiently only. In no case was there any exacerbation of previous symptoms or appearance of any new mental symptoms. Renal functions were assessed in detail in cases 1, 2, 4 and 6 who had been on lithium for more than 3 years. None of these patients showed any glycosuria or proteinuria. Blood urea and serum electrolytes were within the normal range in all cases. There was no case of polyuria, i.e. urinary output exceeding 3 litres per day. All patients could concentrate their urine about 500 mOsm/L after over night fluid deprivation. Serum creatinine varied between 1.0-1.5 mg/100 ml (mean 1.2 mg/100 ml). Creatinine clearance varied from 75-110 ml/min with a mean of 85 ml/min. Quantitative estimation of urinary protein excretion in 24 hours

was in the range of 20-60 mg with 45 mg as mean.

DISCUSSION

In the present study, we have reported our experience of children suffering from bipolar affective psychosis treated with lithium carbonate. For diagnostic purposes, we used the criteria of affective psychosis given in ICD-9 and found them quite satisfactory. These criteria also compared well with that of other study (Weinberg and Brumback, 1976). At the time of inclusion in the study, diagnosis of manic depressive psychosis, bipolar type was established in all cases. However, in cases 4 and 6, other diagnoses were considered initially and only a longitudinal follow up could establish the diagnosis of affective illness. Initial difficulties in the diagnosis of an affective illness in children have also been reported by other workers (Weinberg and Brumback, 1976; Khandelwal *et al.*, 1982; Hassanyeh & Davison, 1980; Brumback and Weinberg, 1977). In cases 1 and 2 other diagnoses were entertained for academic reasons and then subsequently ruled out. Cases 3, 5 and 7 presented with convincing affective symptoms of episodic nature and in them no other diagnosis was considered. Because of the bipolar nature of the illness, all the children were treated with lithium carbonate. Other factors which guided our decision in this direction were recurrent severe episodes causing considerable disorganization of personal and family lives, and presence of affective illness in a near family member. All the children responded well to lithium treatment as described earlier in detail. Many studies (Hassanyeh and Davison, 1980; Brumback and Weinberg, 1977; Feinstein and Wolpert, 1973; Gram and Rafaelsen, 1972; Ansell, 1969) point out that when other thera-

peutic regimes had failed, lithium produced remarkable improvement in children having severe behavioural disturbances. However in many such reports, no definite or strict diagnostic criteria were used. Youngerman and Canino (1978) concluded in their review of lithium carbonate use in children and adolescents that classical symptomatology of alternating mania and depression was clearly responsive to lithium carbonate in all the reviewed cases. Another significant finding in this review was the presence of family history of bipolar affective illness in many cases. We have also observed a similar finding as six of our patients had positive family history. Role of positive family history as a prognostic guide to lithium therapy in adults has been well documented (Mendlewicz *et al.*, 1973). Our results show a similar trend in children also, though in absence of a control sample we are unable to say conclusively if the presence of a family history makes the patient more responsive to lithium therapy. Effective serum lithium concentration were in range of 0.7—1.2 m Eq/L as reported in other studies also (Hassanyeh and Davison, 1980; Brumback and Weinberg, 1977). Case No. 1 continued to experience mild symptoms with serum lithium levels of 0.4-0.6 m Eq/L. However, Frommer (1968) reported response with dosage upto 250 mg/day. Remarkably, all the children tolerated the drug well and experienced only transient side effects viz., nausea, vomiting and tremors. In no case, were we forced to stop lithium due to its side effects. In our study, no child ever experienced exacerbation of depressive features despite the fact that four of our cases have been on lithium prophylaxis for more than 3 years. This finding is in contrast to the findings of some workers (Brumback & Weinberg, 1977; Frommer, 1968) and similar to another one (Hassanyeh and Davison, 1980). Many

of Frommer's cases required addition of a tricyclic antidepressant and in many cases lithium therapy had to be discontinued due to exacerbation of depressive features. In Brumback and Weinberg's series also, five of their six patients showed a similar exacerbation of depression. Electroencephalographic abnormalities like diffuse spike-wave bursts without any clinical seizures have been reported during lithium treatment (Brumback and Weinberg, 1977; Campbell, 1972). However, since we do not have the pre-and post treatment EEG records of all cases, it is difficult to comment on it. Long term effects of lithium in adults on their thyroid functions (Schou *et al.*, 1968) and renal functions (Hestbech *et al.*, 1977; Vestergaard *et al.*, 1979; Khandelwal *et al.*, 1983) have been well reported. However no such study has appeared in cases of children. In our series, four children (S. No. 1, 2, 4 and 6) were investigated in detail regarding their renal functions. As reported earlier, there was no impairment of either tubular or glomerular functions. It has been a very encouraging finding in view of the fact that now more and more children are likely to be put on lithium for its beneficial effects. Schou remarks in a study that children tolerate relatively large doses of the drug because of their high renal lithium clearance, and they seemed to be much less prone to side effects (Youngerman & Canino, 1978.)

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