Indian J. Psychiat. (1980), 22, 304—306

LITHIUM NEUROTOXICITY AT 'THERAPEUTIC' LEVELS A CASE REPORT

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SUMMARY

A case of a young manic patient who developed severe neurotoxicity when on lithium alone has been presented. Investigations did not reveal presence of any infection, electrolyte imbalance or rise in lithium level.

The possibility of lithium producing neurotoxicity at therapeutic levels for as yet unknown reasons is pointed out. It is suggested that this element of risk be considered when starting lithium for therapy or prophylaxis of affective disorders.

Generally, serum levels of 1.0 to 1.5 m Eq/L have been recommended for the treatment of acute mania, and levels of 0.8 to 1.0 m Eq/L for the prophyalxis of affective disorders. Severe intoxication is unusual at serum levels <3.0 m Eq/L and levels ≥ 5.0 m Eq/L can be fatal (Strayhorn and Nash, 1977).

Lithium intoxication at therapeutic serum levels, although rare, is not unknown. Strayhorn and Nash (1977) have reviewed the relevant literature and discussed the possible explanations, namely : (i) synergistic action of lithium with other drugs, (ii) excessive tissue retention of lithium, (iii) loss of sodium through diuretic therapy or dehydration, (iv) old age and infirmity of the patient, (v) a seizure diathesis in the patient, (vi) use of lithium to treat schizophrenia and (vii) concurrent infections.

We present here the case report of a young male manic depressive who developed severe neurotoxicity at "therapeutic" serum level of lithium and in whom the aforementioned "explanations" did not seem to apply.

REPORT

Mr. P. aged 22 yrs. had been having manic depressive attacks since February 1976. On all occasions he was treated at NIMHANS.

The course of the illness was as follows : In February 1976, he had a short spell of depression (nearly three weeks) followed by a manic episode of 14 weeks duration. He was treated with Haloperidol 15-40 mg per day. He had 2 manic episodes in April 1977, and September 1977, of nearly 2 months each, and was treated with haloperidol (20 mg) and Chlorpromazine (400-800 mg) per day. In March 1978 he had an episode of mania followed by a short depressive spell ; both episodes together lasting nearly 3 months. He was treated first with haloperidol (10-30 mg per day) and later with imipramine (150 mg/day) till discharge.

On 12th November 1978, he was admitted for the 5th attack of mania. As the episodes of affective illness were becoming very frequent, we decided to start him on lithium. After initial blood urea, serum creatinine estimations, urine micro-

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scopy and EKG, he was started on lithium carbonate 900 to 1350 mg per day, with a serum level of between 0.8 and 1.1 m Eq/L. At no time was the standard serum lithium level (12 hours after last dose of lithium carbonate) over 1.1 m Eq/L. He improved remarkably and was discharged on 16th December 1978 on lithium carbonate at 1050 mg per day (Lithocarb 150 mg-2-2-3). He was euthymic and in good health at the time of discharge.

He was seen again on 3rd January 1979 when he was euthymic, quite healthy, had only mild tremor of hands. He was advised to continue the same treatment and to report for serum lithium estimation after 2 weeks.

He was brought to the outpatient department on 8.1.1979 with complaints of severe tremors, dizziness, feelings of marked weakness and feeling sleepy.

On examination, he was found to be drowsy, slightly confused and irritable, with definite memory deficits. There was marked tremor of the hands and the speech was dysarthric. Temperature was 37.2°C, there was no dehydration, pulse was 92/min. regular, and blood pressure was 126/84 mm of mercury. Cardiovascular and respiratory systems were normal.

Nervous system examination revealed dysarthric speech, severe tremor of the hands, moderate weakness (Grade III) with hypotonia of all the four limbs. There was mild ataxia and nystagmus. Cerebellar signs were minimal. Reflexes were symmetrically diminished in all the four limbs. Plantars were flexor. There were no signs of meningeal irritation.

He was admitted with a diagnosis of possible lithium toxicity.

Emergency estimation of serum electrolytes revealed—lithium 1.0 mEq/L (11 hrs. after last dose), Sodium 142 mEq/L, Potassium 3.7 mEq/L, Chloride 100 m Eq/L. Hemogram results were as follows : WBC total count=4900/cu mm. differential count=Polys—66%, Lymphocytes=26%, Eosinophils=4%, and Monocytes=4%, ESR=8 mm/hr. E.K.G. and Chest X-rays were normal. A repeat serum lithium within one hour was also 1 m Eq/L.

A lumbar puncture was then performed to exclude encephalitis. The C.S.F. was normal : clear, colourless fluid, cells 2/ cu mm. (Lymphocytes), Protein 26 mg%, Globulin negative, Glucose 55 mg%, Chloride 720 mg%. C.S.F. Lithium absent.

RBC Lithium=0.7 m Eq/L. Serum Lithium 1.6 m Eq/L, giving a lithium ratio of 0.44.

Over the next three days, the patient's condition remained status quo. Lithium was withdrawn and plenty of oral fluids given. He was on no other medication. His sensorium improved over the next one week and by the 10th day of admission, it was quite clear. He continued to have mild tremors of the hand and dysarthric speech. By the end of second week, the muscle power was normal. Tremors of the hand and cerebellar signs were mild, but the speech was disproportionately dysarthric. He could not recall when he came to the hospital, and was amnestic to the first four days of hospital stay and the two days prior to this. As the patient was now euthymic, he was discharged without any medication and was advised to come for follow up every month. During the follow up, his dysarthric speech improved, but there was no total recovery although muscle power was normal and tremors had totally subsided.

He was admitted again in January 1980 for mania and was treated with phenothiazines. His neurological status, but for the residual dysarthria, was normal.

DISCUSSION

Neuroleptic medication like chlorpromazine or haloperidol administered along with lithium can possibly increase the toxicity of lithium (Refkin *et al.*, 1973).

Evidence to such a possibility exists in the reports of Cohen and Cohen (1974). Elderly patients possibly (Van Der Velde, 1971) as also schizophrenics (Shopshin *et al.*, 1970) do not tolerate lithium well. Low sodium intake and excessive loss of sodium can lead to lithium retention and toxicity (Platman & Fieve, 1969). Increased intra-cellular lithium levels have been postulated as leading to lithium toxicity (Elizur *et al.*, 1972). It is clear that none of these usually possible explanations are applicable in our patient.

Intercurrent infections, especially very mild ones, are very difficult to rule out. But the blood counts do not indicate the presence of infection, and a normal C.S.F. makes an encephalitis highly unlikely. We are hence unable to explain this toxicity at therapeutic serum levels.

The fact that a rare patient who even when fairly stable on lithium can develop toxicity for as yet unknown reasons, makes it necessary for us to consider this new element of risk when considering lithium for therapy or for prophylaxis.

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