

LITHIUM TOXICITY - A DESCRIPTIVE STUDY

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ABSTRACT

Lithium is the treatment for acute mania and bipolar disorders. Ever since its introduction in the psychiatric arsenal, case reports of toxicity have been appearing in the literature at regular intervals. This study was thus carried out to study the presentation and associated features of lithium toxicity. In this retrospective study, case record files of all patients suspected to have developed lithium toxicity during a five year period were retrieved. It was found that toxicity presented most commonly with cerebellar symptoms and appeared at lower serum levels. Lithium could be restarted albeit at a lower dose and with a gradual titration in a number of cases.

Key words : Lithium, toxicity, cerebellar, rechallenge, therapeutic

Lithium remains the paradigmatic treatment for acute mania and prophylaxis of bipolar disorders (Post, 1995). Lithium has a low therapeutic index and case reports abound in published literature about its toxic effects (e.g. Andrade et al., 1987, 1988; Kumar et al., 1999; Sampath et al., 1980, Cohen and Cohen, 1974; Thomas, 1979, Rifkin et al., 1973, Thornton and Pray, 1975; Shopsin and Gershon, 1973; Gangadhar et al., 1993). In a number of them (e.g. Andrade et al., 1987, 1988, Kumar et al., 1999; Sampath et al., 1980, Gangadhar et al., 1993) the toxicity was evidenced in the therapeutic range. Various precipitating factors like concomitant antipsychotic administration (e.g. Cohen and Cohen, 1974, Thomas, 1979; Rifkin et al., 1973, Shopsin and Gershon, 1973; Thornton and Pray, 1975), organicity (Shopsin and Gershon, 1973; Thornton and Pray, 1975; Stayhorn and Nash, 1977) and a diagnosis of schizophrenia (Shopsin and Gershon, 1973) were put forward to account for the toxicity. Though there have been a number of reviews (e.g. Stayhorn and Nash, 1977; Schou, 1984, Roy et al., 1999) attempting to synthesize the findings of the case reports there have been

few studies on assessing the toxicity (Baastrup et al., 1976; Goldney and Spence, 1986). Both these studies were retrospective in nature and attempted to find out whether lithium toxicity occurred more frequently when combined with antipsychotic drugs. This study was thus carried out to study the presentation and associated features of Lithium toxicity.

MATERIAL AND METHOD

This was a retrospective study conducted in Central Institute of Psychiatry, Ranchi. This is a tertiary referral centre for psychiatric problems catering to the entire Eastern Indian population.

Patients are admitted in different wards according to the admitting unit and gender of the patient. A twenty four hour report is prepared daily in each ward in the night and contains the details of all patients who are a management problem or have physical problems.

The daily reports of all wards were screened by the members of the research team for the period between 1st August 1993 to 31st July 1998. The date and the name of those

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patients were noted who were mentioned as having either probable lithium toxicity or had descriptions suggestive of toxicity such as nausea, vomiting, diarrhea, tremors, unsteady gait, unclear speech or confusion. The cases in which the reports suggested a clear cut extrapyramidal syndrome were excluded from the study.

The case record files of the noted patients were removed from the record section of the institute by the registration number obtained by tallying the patients name and date from the admission register. Members of the research team reviewed the case record files and a diagnosis was ascribed to the physical problem. In case of any doubt, the case was discussed amongst members of the research team and a consensus diagnosis was reached at.

A diagnosis of Lithium toxicity was made if the patient was receiving Lithium and had signs and symptoms suggestive of lithium toxicity (Jefferson and Greist, 1995) which could not be explained otherwise.

RESULTS

A total of 38 patients were identified as having probable lithium toxicity. Out of these, files could be traced for 36 patients. On reviewing the files, a diagnosis of lithium toxicity was ascribed to 18 cases. 3 cases were excluded, as serum lithium levels were not recorded in the files leaving a final sample size of 15. The details of the sample are given in table 1.

This consisted of 10 males and 5 females. The diagnosis was first episode mania in 2 cases, bipolar mania in 12 cases and bipolar depression in 1 case. The mean daily lithium dosage was 1000 ± 209.6 with a median and mode of 900 mg and a range of 900-1650 mg daily. The mean age of the sample was 33.4 ± 10.93 with a range of 19 to 55 years.

The concomitant treatment at the time of toxicity was antipsychotics in 11 cases (Haloperidol in 9 and Chlorpromazine in 2), antidepressants and haloperidol in 1 case, ECT

and haloperidol in 1 case and a combination of lithium, carbamazepine and chlorpromazine in one case. The average daily dose of antipsychotics was 10.2 ± 6.12 mg in haloperidol equivalents (range 0-20 mg).

The interval between initiation or hiking of lithium dose and the appearance of features of toxicity was 11.47 days with a median of 10 and a mode of 7 days. The range was 5-45 days. On removing the outlier of 45 days, the median was 7 days and the mean was 9 days.

The mean lithium level recorded in the file immediately after toxicity was suspected was 1.44 ± 0.66 (range 0.3-2.5) m mol/L. This serum lithium level was obtained using flame photometry method. The drugs were stopped and serum lithium was obtained the next day.

Patients with serum lithium levels less than 1.5 m mol/L were significantly younger than those with serum lithium level more than 1.5 m mol/L (mean age was 26.13 ± 5.25 years in patients with serum lithium level less than 1.5 compared to 41.72 ± 9.76 in those with serum lithium level more than 1.5, 't' test, $p=0.002$). There was no significant difference in sex, haloperidol dose, lithium dose, precipitating factor and rechallenge of lithium between patients with serum level more than 1.5 m mol/L and less than 1.5 m mol/L.

Possible precipitating factors were identified in 3 patients. This consisted of NSAID administration for two days prior to symptoms in 1 patient and low grade fever for 2-3 days prior to symptoms in 2 patients.

The toxicity features were divided into two groups - neurotoxicity and others. The neurotoxicity group had cerebellar and/or cortical manifestations. Cerebellar signs consisted of a mixture of ataxia, impaired tandem walk and finger nose test, slurred speech, hypotonia, pendular jerks and coarse tremors. The cortical signs consisted of a mixture of confusion, exaggerated jerks, seizures and hypertonia. All other presentations such as nausea, vomiting, loose motions, loss of appetite were grouped together in the second group.

TABLE
SHOWING THE DEMOGRAPHIC, TREATMENT AND TOXICITY FEATURES OF THE SAMPLE

| Age | Sex | Haloperidol dose | Lithium dose (mg) | Lithium level mmol/L | Ppt. Factor | Rechallenge | Rechallenge dose (mg) | Rechallenge outcome | Final Outcome | Symptoms of toxicity |
|-----|--------|------------------|-------------------|----------------------|-------------|-------------|-----------------------|---------------------|---------------|--|
| 20 | Male | 15 | 900 | 0.3 | | Yes | 900 | No S/E | F.R. | Tremor, nystag |
| 30 | Male | 10 | 900 | 0.5 | | No | X | X | F.R. | Seizure, Confusion, ataxia, dysarthria, imp tan, nystag. |
| 26 | Male | 5 | 900 | 0.7 | Fever | Yes | 900 | No S/E | F.R. | Dysarthria, ataxia, tremor, imp. tan., dys. |
| 32 | Female | 15 | 900 | 0.9 | | Yes | 600 | S/E | F.R. | Confusion, drowsy, dys. ataxia |
| 32 | Male | 15 | 1200 | 0.9 | | No | X | X | F.R. | Vomiting, confusion, ataxia, nystag. |
| 19 | Male | 15 | 1650 | 1.3 | | Yes | 900 | No S/E | F.R. | Confusion, loose motion, tremors |
| 28 | Male | 20 | 1050 | 1.5 | | No f/up | X | X | F.R. | Hypotonia, nystag., ataxia, pen. tremors |
| 22 | Female | 5 | 1200 | 1.5 | | No | X | X | F.R. | Tremors, ataxia, confusion, sedation |
| 37 | Male | 6.5 | 900 | 1.6 | | Yes | 600 | S/E | F.R. | Dysarthria, ataxia, nystagmus |
| 45 | Female | 10 | 900 | 1.8 | | No f/up | X | X | Sym | Ataxia, dysarthria, confusion, hypertonia, nystag., pen. |
| 42 | Female | 20 | 900 | 1.9 | Fever | Yes | 750 | No S/E | F.R. | Confusion, tremors, dysarthria, ataxia |
| 50 | Male | 0 | 900 | 2.0 | NSAID | No | X | X | F.R. | Nausea, decreased appetite and loose motion |
| 25 | Male | 6.5 | 900 | 2.0 | | Yes | 1050 | No S/E | F.R. | Dys., tremor, nystag |
| 38 | Female | 5 | 900 | 2.2 | | No | X | X | F.R. | Nausea, loose motion |
| 55 | Male | 5 | 900 | 2.5 | | No | X | X | F.R. | Decreased appetite, loose motions |

F/up - Follow up; S/E - Side effects; F.R. - Full recovery; Sym - Symptomatic at discharge; Rechallenge - Rechallenge; NSAID - Diclofenac tablets; Nystag. - nystagmus; pen. - pendular jerks; imp tan - impaired tandem walk; dys - dysdiadokinesis; tremors - Coarse tremor

A total of 12 patients presented with neurological symptoms for toxicity out of which 7 displayed cortical symptoms and all 12 displayed cerebellar symptoms. The mean serum lithium level was significantly less in patients with cerebellar symptoms than those without (mean serum lithium level was 1.24 ± 0.57 in patients with cerebellar symptoms and 2.23 ± 0.25 in those without cerebellar symptoms, 't' test, $p=0.012$). There was no significant difference in the mean serum lithium levels in patients with or without cortical or other symptoms ('t' test, $p=ns$)

Out of the 15 patients, 2 were lost on follow up, 6 were not rechallenged with lithium and 7 were readministered lithium. Out of these 7, 2 patients were those who had a precipitating factor. For rechallenge, the lithium was started at 600 mg and hiked at 150 mg intervals every

week. Out of the 7, three patients were established on the same dose prior to toxicity without a recurrence. All three had only cerebellar manifestation and one of them had an antecedent in terms of fever. Out of the remaining four patients, 2 redeveloped similar toxicity on a lesser dose. Both of them had neurological manifestations and none had antecedents. The remaining two patients were maintained at 150 mg less than the dose at which toxicity was experienced. One of them had an antecedent and both had neurological symptoms.

The three patients excluded due to lack of serum lithium levels consisted of 2 males and 1 female. They were receiving lithium in the range of 900 - 1350 mg daily along with haloperidol. All three had both cortical and cerebellar symptoms. One patient was reexposed to lithium

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and did not develop any toxicity.

DISCUSSION

Most of our patients were on combination with antipsychotics which has been postulated to be a risk factor for neurotoxicity (Cohen and Cohen, 1974; Thomas, 1979; Rifkin et al., 1973; Thornton and Pray, 1975). All of these were case reports with haloperidol used in doses upto 100 mg and lithium upto 2400 mg. Furthermore, the case of Cohen and Cohen (1974) had fever also. This issue was addressed in retrospective studies by Baastrup et al. (1976) and Goldney and Spence (1986) who found no evidence of lithium toxicity in patients with concurrent neuroleptic administration. All our cases had daily haloperidol equivalent doses of less than 20 mg per day and the modal lithium dose of 900 mg. Thus it is quite unlikely that the toxicity in our patients was due to a combination of neuroleptics and lithium.

Except for one case, the modal duration of interval between toxicity and hiking the dose was 7 days which agrees with the pharmacokinetic five half lives of lithium to attain the new serum level. Thus it could be that there exists individualized threshold levels for the occurrence of toxicity. This is borne by the finding that two patients could be maintained without toxicity at a lesser dose. Of interest is the finding that three patients could be maintained on the same dose when the dosage was built gradually. Thus it is not only the threshold which is important but also the rate at which it is attained. Schou (1984) reports restarting of lithium in three patients without any signs of lowered tolerance or aggravation of neurological disturbances. Thus an attempt of lithium rechallenge may be attempted on patients experiencing toxicity.

Another finding of interest is that cerebellar symptoms were the most common presentation and occurred at a significantly lesser serum level. Cerebellar symptoms at therapeutic serum levels have been reported as features of toxicity (Andrade et al., 1987, 1988; Kumar et al., 1999; Sampath et al., 1980) and a

recent review (Roy et al., 1999) concluded that lithium had a tropism specific to the cerebellum. Thus it seems that toxicity developing at lower serum levels predisposes a person to develop the cerebellar form.

Fourteen of the fifteen patients improved. This suggests that if prompt action is undertaken, the signs of lithium toxicity are reversible. In accordance with the finding of Schou (1984) and Andrade et al. (1987, 1988) the remnant deficit in the lone case was cerebellar in nature. This good prognosis could also be due to the fact that in most of the cases the toxicity occurred at therapeutic serum levels and in only four cases was the level more than 2 mmo/L.

In the majority of the cases (80%) no precipitating factor could be identified. Furthermore, the lithium level was mostly in the therapeutic range. One must keep in mind that the serum was drawn immediately after suspicion of toxicity and thus this estimation was done less than twelve hours after the last dose. In most of the cases it was done approximately six hours after the last dose and thus the twelve hour serum lithium values might have been lower. This suggests that the toxicity in these patients might be idiosyncratic in nature. In the case reported by Gangadhar et al. (1993), even though the serum lithium level was at the lower end of therapeutic range, RBC lithium levels revealed high intracellular concentrations. It has been discussed by Bell et al. (1993) that intraerythrocyte lithium levels correlate better with cerebral levels and blood cell : plasma ratio vary from individual to individual with some individuals genetically predisposed to take up more lithium intracellularly from a given dose than others (Dorus et al 1975). This might be the explanation for the development of neurotoxicity at the therapeutic serum levels. Lithium level monitoring as well as the RBC : Plasma lithium ratio may thus be a better indicator of neurotoxicity.

In conclusion, our study reports that the occurrence of toxicity after lithium administration at therapeutic levels might be idiosyncratic. There are individual variations in the threshold for

the appearance of toxicity and that gradual titration may be required to achieve that threshold. In younger patients, toxicity appears at lower serum lithium levels. If toxicity occurs at a therapeutic level, lithium may be attempted to be reintroduced gradually. Cerebellar symptoms as manifestation of toxicity are the most common manifestation and appear at lower serum lithium levels. Lithium toxicity may be reversible if tackled early.

One must keep in mind that the study was retrospective in design and some cases might have been missed during the review of the daily reports. The sample size was also too small to arrive at a definitive conclusion. However, as the drugs were used in the dosage and combination commonly used in clinical settings, this low sample size might reflect the idiosyncratic nature of the toxicity.

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