Indian J. Psychiat., 1997, 39 (3), 251-255

INCREASED RISK OF OCCURRENCE OF NEUROLEPTIC MALIGNANT SYNDROME ON COMBINED TREATMENT WITH LITHIUM AND NEUROLEPTIC

P. JOHN ALEXANDER & RANJI MATHAI THOMAS

ABSTRACT

Whether there is an increased risk of occurrence of neuroleptic malignant syndrome (NMS) on combined treatment with lithium and neuroleptic is a controversial issue. Patients seen in a general psychiatry unit of a university hospital in India were prospectively screened for NMS over a 2 year period. Diagnosis of NMS was made on operational criteria and the details of treatment at the time of occurrence of NMS were collected systematically. Eight cases of NMS were identified during the period of the study, out of which 5 (62.5%) were taking lithium and a neuroleptic together at the time of occurrence of NMS. The high prevalence of patients on lithium and neuroleptic concomitantly in our sample of NMS, and the similar findings in many of the earlier prospective studies, makes it possible to speculate whether there is an association between combined use of lithium and neuroleptic and occurrence of NMS. Findings are discussed.

Key words : NMS, lithium, neuroleptics

Neuroleptic malignant syndrome (NMS) is a rare but potentially lethal condition, estimated to occur in 0.02% to 3.23% of patients treated with neuroleptics (Addonizio & Susman, 1991; Carrof & Mann, 1993). Though a variety of risk factors like use of high potency neuroleptics, rapid dose escalation, administration of parenteral neuroleptics, use of high dose of neuroleptics, organic brain disorder, affective disorder, agitation etc. have been reported to increase the risk of NMS, consensus about aetiopathogenesis is elusive (Levenson, 1985; Addonizio & Susman, 1991; Carroff & Mann, 1993;).

The role of lithium (when used concurrently with neuroleptic) in increasing the risk of NMS is a controversial issue. There are many case reports of increased neurotoxicity and NMS occurring with a combination of lithium and neuroleptics, especially with haloperidol (Cohen & Cohen, 1974; Loudon & Waring, 1976; Spring & Frankel, 1991). Retrospective analysis have found that upto 50% of patients who developed NMS were on treatment with lithium and neuroleptics at the time of occurrence of NMS (Addibuzui et al., 1986; Keck et al., 1989). Also, Keck et al. (1987) and Rosebush & Stewart (1988) found on prospective studies that 50% or more of patients with NMS were taking lithium along with a neuroleptic when they developed NMS. These authors found that NMS can occur when lithium is used with neuroleptics other than haloperidol also. However, some retrospective studies didn't find any evidence of neurotoxicity with concurrent use of lithium and neuroleptics (Baastrup et al., 1976; Goldney & Spence, 1986). A variety of methodological factors like the retrospective design, imprecise diagnosis of NMS, non-control of other variables etc. could

have confounded the results of many studies.

In Indian literature there is a paucity of reports on NMS (Thomas et al., 1993). Epidemiological studies from various countries have shown that bipolar disorder has an estimated life time risk of around 1% (Goodwin & Jamison, 1990). In view of the large population of India and enormous number of patients exposed to this treatment combination of litium and neuroleptic/s, we conducted a prospective study about the association of combined use of lithium and neuroleptic and the occurrence of NMS.

MATERIAL & METHOD

All the cases seen at psychiatry unit of Kasturba Hospital, Manipal from January 1994 to December 1995 were carefully assessed for NMS. This psychiatry unit runs its outpatient clinic three times a week and on these days besides outdoor patients attending the section, the unit also saw all the inpatient referrals from other departments and the emergency calls. This is a referral hospital, catering to a geographical area of two southern states of India. The present report is a part of study to assess the prevalence and risk factors for NMS.

The diagnosis of NMS was made when patients exposed in the past 1 week to neuroleptic (4 weeks in case of depot neuroleptic preparation) had fever, rigidity, altered consciousness and autonomic instability which couldn't be accounted by any other physical or mental illness (Carroff et al., 1991). All the patients were also seen by a consultant neurologist and appropriate investigations to rule out neurological illness to account for these symptoms were done. When clinically indicated, patients were referred to other consultants and relevant investigations tc rule out other physical disorders were carried out. Details of the drug treatment was collected from the close relative/s, available prescriptions at the time of admission and from the patients after they recovered from the episode of NMS. Informed consent was obtained from all the patients for the use of clinical records.

RESULTS

Eight cases who met the operational criteria of NMS were identified. The age, sex, ICD-10 psychiatric diagnosis (WHO, 1992) and details of drug treatment of the 8 patients are shown in table . The age range of the patients was from 21 to 63 years. Male and female were equally present in the sample. Seven (87.5%) of the patients were suffering from affective disorder. Except one all the other patients were on treatment from practising psychiatrists or other doctors. A diagnosis of NMS as a possibility was mentioned in only 2 of the referrals by the treating doctor.

Out of the 8 patients, 5 were taking lithium and a neuroleptic concomitantly when they developed NMS. Serum lithium level was within the therapeutic range in all the 5 patients on lithium (range being 0.4 milliequivalents to 1.2 milliequivalents) which was done at varying points of time (24 hours to 72 hours after the last dose of lithium).

DISCUSSION

Our diagnosis of NMS was made on operational criteria of Caroff et al. (1991) and also met the research criteria proposed by DSM-IV (APA, 1994). We have tried to exclude by careful evaluation other systemic and neuropsychiatric illnesses producing the symptoms of NMS. It has been observed that NMS be over diagnosed if broad criteria are applied as other medical causes may account for the symptoms necessary for the diagnoses of NMS (Levinson & Simpson, 1986).

It may be difficult in some cases to distinguish between lithium neurotoxicity and NMS, since lithium in therapeutic range is known to produce neurotoxicity (Schou, 1984). In some patients there can be features of both lithium toxicity and NMS (Cohen & Cohen, 1984). However, lithium toxicity is not usually associated with fever and typically its neurotoxicity

manifests with weakness, extreme lethargy, cerebellar signs, fasciculations, myoclonic jerks and seizure (Schou, 1984; Sansone & Zeigler, 1985; Rosebush & Stewart, 1989). Thus, based on the symptomatology, in most cases it is possible to distinguish lithium toxicity and NMS. It is unlikely that any of our patient primarily had lithium toxicity.

The findings of the present study is in concordance with observations in literature that a majority of patients who develop NMS are on haloperidol. However, this may reflect prescribing practice rather than any specific risk for haloperidol (Addonizio & Susman, 1991). Lithium in combination with other neuroleptics is also known to produce NMS (Addonizio & Susman, 1991; Carroff & Mann, 1993).

Keck et al. (1987) found 6 cases of NMS, 3 were on lithium and neuroleptic. The authors opined that lithium might have increased the frequency of NMS. Similarly, Rosebush et al. (1989) in their study found that lithium was being used in 58% of those who developed NMS, enabling them to raise the question of an association between concomitant lithium and neuroleptic use and development of NMS. These findings make it possible to speculate that there is an increased risk of occurrence of NMS when patients are treated with a combination of lithium and antipsychotic/s.

A variety of ways of which lithium can increase the risk of development of NMS have been proposed (Rosebush et al., 1989; Addonizio & Susman, 1991). Lithium alone can cause extrapyramidal (EPS) symptoms (Shopsin & Gershon, 1975) and it is known that it enhances the EPS produced by neuroleptics (Addonizio, 1985). It may also increase the

TABLE
CHARACTERISTICS OF PATIENTS WITH NEUROLEPTC MALIGNANT SYNDROME

No.	Age	Sex	Psychiatric Diagnosis	Medications Per Day
1	30	F	Unspecified nonorganic psychosis (postpartum)	Chlorpromazine - 20mg
2	21	M	B.A.D. Currently Mania	Lithium 900 mg+ Thioridazine 100 mg
3	24	M	B.A.D. Currently Mania	Lithium 900 mg+ Haloperidol 15 mg
4	62	M	B.A.D. Currently Mania	Lithium 600 mg + Haloperidol 5mg+ Carbamazepine 600 mg
5	55	M	B.A.D. Currently Mania	Lithium 600 mg + Haloperidol 20 mg
6	63	F	B.A.D. Currently Mania	Lithium 900mg + Haloperidol 50mg
7	22	F	Severe Depressive Episode (postpartum)	Amoxapine 100 mg
8	26	F	Severe Depressive Episode (postpartum)	Trifluperazine 20mg + Chlopromazine 100 mg+ Trihexyphenidyl 4 mg

B.A.D. Bipolar Affective Disorder

chance of a hypodopaminergic state and this is implicated in the pathogenesis of NMS (Addonizio & Susman, 1991). Also, these drugs by interaction may alter intercellular and serum levels of both the drugs thereby increasing the risk of NMS. Lithium toxicity can predispose to the development of NMS by electrolyte imbalance and renal dysfunction. Even in nontoxic range lithium by inducing polyuria, can produce fluid and electrolyte imbalance and increase the risk for NMS (Addonizio & Susman, 1991; Carroff & Mann, 1993).

Alternatively, it can be conceptualised that lithium is likely to be used in affective disorder and since these patients are likely to get agitated and excited, all these factors are proposed risks for NMS, the association between lithium and NMS may be spurious. Retrospective studies have found that there are significantly more patients with affective disorders in NMS than in controls (Addonizio et al., 1986; Keck et al., 1989). In the present study also, 87.5% of patients were of affective disorder.

However, it can't be concluded definitely from our study that lithium neuroleptic combination increases the risk of NMS. In clinical practice these drugs are often used in combination with no untoward effects. Two retrospective studies (Baastrup et al., 1976; Goldney & Spence, 1986) found no significant risk of neurotoxicity or NMS with this combination. Similarly, retrospective studies for risk factors of NMS using control groups have found no significantly increased use of lithium in NMS patients compared to controls who didn't develop NMS (Addonizio et al., 1986; Keck et al., 1989). Deng et al. (1990) in a prospective study of 7 years identified 12 cases of NMS and found that only 1 was on lithium and thus concluded that lithium is not a significant risk factor for NMS.

The confounding effects of risk factor for NMS need study using multivariate statistical techniques. Unless large sample size are collected using collaborative effort from multiple centres, it may be difficult to precisely pin point the risk factors for NMS, including that of lithium.

REFERENCES

Addonizio, G. (1985) Rapid induction of extrapyramidal side effects with combined use of lithium and neuroleptics. *Journal of Clinical Psychopharmacology,* 5, 296-298.

Addonizio, G., Susman, V.L. & Roth, S.D. (1986) Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. *American Journal of Psychiatry,* 143, 1587-1590.

Addonizio, G. & Susman, V.L. (1991) Neuroleptic malignant syndrome. New York: Mosby year Book Inc.

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. Fourth edition, Washington, DC.

Baastrup, P.C., Hollangel, P., Sorensen, R. & Schou, M. (1976) Adverse reactions in treatment with lithium carbonate and haloperidol. *Journal of American Medical Association,* 236, 2645-2646.

Carroff, S.N. & Mann, S.C. (1993) Neuroleptic Malignant syndrome. *Medical Clinics of North America,* 77, 185-202.

Carroff. S.N., Mann, S.C. & Lazarus, A. (1991) Neuroleptic malignant syndrome: diagnostic issues. *Psychiatric Annals* 21, 130-147.

Cohen, W.J. & Cohen, N.H. (1974) Lithium carbonate, haloperidol and irreversible brain damage. *Journal of American Medical Association,* 230, 1283-1287.

Deng, M.Z., Chen, G.Q. & Phillips, M.R. (1990) Neuroleptic malignant syndrome in 12 of 9, 792 Chinese inpatients exposed to neuroleptic: a prospective study. *American Journal of Psychiatry,* 147, 1149-1155.

Goldney, R.D. & Spence, N.D. (1986) Safety of the combination of lithium and neuroleptic drugs. *American Journal of Psychiatry,* 143, 882-884.

Goodwin, F.K. & Jamison, K.R. (1990) Manic Depressive Illness. New York : Oxford University Press.

Keck, P.E. Jr., Pope, H.G. Jr.; & McElroy,

S.L. (1987) Frequency and presentation of neuroleptic malignant syndrome: a prospective study. *American Journal of Psychiatry,* 144, 1344-1346.

Keck. P.E. Jr., Pope, H.E. Jr., Cohen, B.M., McElroy, S.L. & Neirenberg, A.A. (1989) Risk factors for neuroleptic malignant syndrome. *Archives of General Psychiatry,* 46, 914-918.

Levenson, J.L. (1985) Neuroleptic malignant syndrome. *American Journal of Psychiatry,* 142, 1137-1145.

Levinson, D.F. & Simpson, G.M. (1986) Neuroleptic induced extrapyramidal symptoms with fever. *Archives of General Psychiatry,* 43, 839-848.

Loudon, J.B. & Waring, H. (1976) Toxic reactions to lithium and haloperidol. *Lancet,* 11, 1088.

Rosebush, P. & Stewart, T. (1989) A prospective analysis of 25 episodes of neuroleptic malignant syndrome. *American Journal of Psychiatry,* 146, 717-725.

Sansone, M.E. & Ziegler, D.K. (1985) Lithium toxicity: a review of neurologic complications. *Clinical Neuropharmacology,* 8, 242-248.

Schou, M. (1984) Long-lasting neurological sequale after lithium intoxication. *Acta Psychiatrica Scandinavica,* 70 594-602.

Shopsin, B. & Gershon, S. (1975) Cogwheel rigidity related to lithium maintenance. *American Journal of Psychiatry,* 132, 536-538.

Spring, G. & Frankel, M. (1981) New data on lithium and haloperidol incompatibility. *American Journal of Psychiatry,* 138, 818-821.

Thomas, K., Rajeev, K.K., Abraham, O.C., Sud, A. & Cherian, A.M. (1993) Management of neuroleptic malignant syndrome- a series of 8 cases. *Journal of Association of Physicians of India,* 41, 91-93.

World Health Organisation (1992) The ICD-10 classification of mental and behavioural disorders, clinical description and diagnostic guidelines, Geneva: World Health Organisation.

P JOHN ALEXANDER, M.D., Associate Professor, RANJI MATHAI THOMAS, M.B.B.S., Resident , Department of Psychiatry. Kasturba Medical College, Manipal 576 119, Karnataka.

Correspondence