Indian J. Psychiat., 1995, 37(1), 9-12.

ONCE-DAILY VERSUS DIVIDED DOSAGE LITHIUM THERAPY IN ACUTE MANIA

K.P.SURESH, K.M.R.PRASAD, RAJESH MOHAN, CHITTARANJAN ANDRADE, M.V.ASHOK, S.K.CHATURVEDI, K.N.SREENIVAS

The aim of the study was to compare once-daily with divided dosage lithium treatment in acute mania. In 79 retrospectively studied subjects who met the DSM III-R criteria for mania, 26 independent and dependent variables were analyzed. The two groups of patients (categorized according to dosage schedule) were broadly comparable with respect to demographic and clinical characteristics. The two groups also did not differ on the outcome measures of lithium efficacy and lithium adverse effects. It is concluded that single dose lithium therapy is clinically comparable with divided dose lithium therapy in acute mania. Possible advantages of switching over to once-daily lithium regimes are discussed.

Key words: lithium, acute mania.

INTRODUCTION

Lithium is the cornerstone in the treatment of a manic episode and in the prophylaxis against mood swings in bipolar affective disorder. Its efficacy in this respect is well established. In India, lithium is usually given daily in two or three divided doses while in many European countries a single daily dose is the preferred regimen (Grof et al, 1980; Schou et al, 1982; Kehoe & Mander, 1992; Bramble, 1992). Whereas currently trials are being conducted on the usefulness of lithium administration on alternate days (Jensen et al, 1990), it is paradoxical that most of the psychiatrists in our country are not even using single dose lithium therapy.

In this study, we therefore compared acutely manic subjects receiving single dose lithium with those receiving divided dosage in order to assess differences, if any, in terms of efficacy and adverse effects. The main hypothesis addressed was that once daily lithium would be associated with equivalent therapeutic outcome and equivalent or fewer side effects compared to divided dose lithium.

MATERIALS AND METHODS

This study was a retrospective chart review of patients from a single clinical unit in an urban, teaching, postgraduate psychiatric institute. Subjects who had registered between January 1991 and December 1992, who met the DSM-III R (American Psychiatric Association, 1987) criteria for acute mania, and who were on therapeutic lithium, were included. Since a rater would have to systematically sift through reams of case notes, it would be impossible for him to remain blind to the lithium dosage schedule. Hence, the charts were evaluated by not one but three raters (KPS, RM & KMRP).

All decisions were based on mutual agreement, and data were recorded on a semi-structured proforma. It was hoped this process would reduce potential bias, if any, in ratings.

Seventy nine subjects met the study criteria; of these, 39 had received single dose lithium and 40 had received divided dose lithium. Fifteen independent variables (demographic and clinical such as age, sex, previous episodes, family history, previous lithium response, symptom profile etc), and eleven dependent variables (lithium dose, serum level, need for additional treatment, adverse drug reactions etc) were studied.

Different variables were operationalized as follows: Lithium dose was defined as the maximum dose (during acute therapy) that was sustained in order to obtain treatment response. The serum lithium level at this dose was recorded. The mean duration of the episode after starting lithium was the time from starting lithium to the onset of euthymia.

Additional treatment was defined as minimal (only SOS injections, during the acute phase), moderate (addition of neuroleptics for a short duration, lithium being the principal drug) and much (neuroleptics / ECT being the principal therapy, with lithium being the adjunct). Adverse drug reactions like gastritis, tremors, polyuria, hypothyroidism etc., were rated only if they were clearly recorded in the case file as being due to lithium. The duration of hospitalization was directly read off from the charts; fitness for discharge in these patients had been based on the clinical judgement of three consultant psychiatrists.

The two groups were compared with respect to the above variables using the Chi square and Fisher's exact probability two tailed tests for categorical data,

and the independent sample t test for quantitative data. The Mann-Whitney U test was used when the assumptions for parametric statistical testing were not met.

RESULTS

Sample description:

Subjects who were on single dose lithium (n= 39) had a mean age of thirty one years and the male:female ratio was 7:1. The mean age of divided dose lithium subjects (n = 40) was twenty nine years and the male:female ratio was 1.6:1. Though the mean age in the two groups was comparable, there was a significantly greater proportion of females in the divided dose group.

The two groups were comparable in the total number of affective episodes, but the single dose group had experienced significantly more depressive episodes (Table 1). The groups were comparable with respect to family history of affective disorder and of non-affective psychosis and with respect to past history of lithium response. The two groups did not differ significantly with respect to the clinical features of the index episode of mania.

The two groups did not differ significantly in any of the 3 categories of dependent variable examined. These categories were lithium dose and level characteristics, efficacy measures and adverse effect measures (Table 2).

Table 1
Demographic and clinical characteristics

Variables	Single dose (n=39)	Divided dose (n=40)	Significance
1. Age (years) Mean ± SD	31.1 ± 11.1	28.9 ± 10.6	t=0.88; df 77 p> 0.10
2. Sex: male	34	24	X^2=5.45; df 1
female	5	16	p<0.02
3. Past history of mania	22 (56.4)	21 (52.5)	X^2=0.2; df 1 p >0.1
4.Past history of depression	12 (30.7)	4 (10.0)	X^2=4.07; df 1 p <0.05
5. Family history of affective disorder	3 (7.7)	7 (17.5)	FEP >0.1
6. Family history of non-affective psychosis	8 (20.5)	5 (12.5)	X^2=0.4.43; df 1 p >0.1
7.Mean (± SD) duration of episode before starting lithium (in days)	56.8± 88.17	62.9± 63.6	Mann-Whitney U test, Z=1.76 p >0.05
8. Past history of lithium response	0 (0)	2 (5.0)	FEP> 0.1

For variables 2, 3, 4, 5, 6 and 8 figures refer to number of cases

Table 2
Dependent variables

Variables	Single dose (n=39)	Divided dose (n=40)	Significance
1. Lithium (mg/day)	1046.2± 166.8	1095.5± 209.9	t=1.14; df 77 p >0.2
2. Serum lithium level (meq/L)	0.7± 0.2	0.8 ± 0.2	t=1.09; df 49 p >0.2
3. Mean (SD) duration of episode after starting lithium (in days)	29.3± 23.1	25.8 ± 21.8	Z=0.4, p> 0.5
4. Mean duration of hospitalization (in days)	28.0± 14.9	34.0 ± 20.9	Z=1.02, p>0.2
5. Need for additional treatment	30 (76.9)	35 (87.5)	X^2=0.88; df 1 p >0.2
6. Nature of additional treatment			
Nil	9 (23.1)	5 (12.5)	
Minimal	9 (23.1)	5 (12.5)	FEP>0.05
Moderate	19 (48.7)	24 (60.0)	p >0.1
Much	2 (5.1)	6 (15.0)	
7. Adverse reactions	3 (7.7)	7 (17.5)	X^2=1.03; df 1 p >0.2
8. Need to decrease lithium dose	0 (0.0)	3 (7.5)	FEP >0.05 p> 0.1
9. Need to stop lithium	1 (2.6)	2 (5.0)	FEP> 0.05 p >0.1
10. Need to change lithium dosage schedule	0 (0.0)	3 (7.5)	FEP>0.05 p >0.1

For variables 5 to10 figures refer to number of cases; figures within brackets denote percentages.

Since sex distribution differed significantly between the two groups, the effect of sex on the dependent variables was analyzed to ascertain whether it could have caused a bias. It was found that all dependent measures were independent of sex. Likewise, the greater number of depressive episodes in single dose group was found not to influence the results.

DISCUSSION

The results of the study indicate that single dose lithium is comparable to divided dose lithium therapy in acute mania. These results are in keeping with the results of many other studies (Perry et al, 1981; Muir et al, 1989). Most studies have looked at the renal side effects of long term lithium therapy in single daily and divided dose regimens. Perry et al (1981) found no significant difference between the two groups with respect to serum half-lives or renal lithium clearance levels and concluded that the average steady state serum lithium concentration is unchanged by conversion to single daily doses. Moreover, if given once daily, a higher 12 hour serum lithium concentration can be achieved, and it is this concentration that is believed to correlate with the therapeutic efficacy of lithium (Amdisen, 1975). In this study, single dose subjects needed less dose per day compared to divided dose subjects, though the finding did not reach statistical significance.

Studies have shown that the mean exposure to lithium in the two regimens is about the same, if measured as the area under the two different curves of serum lithium per 24 hours. This is due to a diurnal variation in renal clearance, which is lower at night (Lauritsen et al, 1981), when the lithium concentration would be high if the drug were administered in a single evening dose.

Another advantage of single dose lithium at night is that for at least 12 hours during the day, the serum level falls below the 12 hour concentration, which is believed to decrease the polyuria associated with lithium therapy (Plenge & Mellerup, 1986).

The majority of adverse drug reactions in our subjects were lithium induced tremors. These occurred less in single dose subjects, though not to a statistically significant extent. Incidentally, observations of fewer adverse reactions and better acceptance of single dose lithium are similar to those for most other psychotropics, e.g, tricyclic antidepressants. The single most important advantage of single dose lithium is better drug compliance. Taking lithium two or three times a day is obviously less convenient, especially for working individuals, than taking a single night dose. The psychological effects of being reminded of the presence of a mental illness twice or thrice a day may also be more damaging.

In conclusion, single dose lithium therapy was found to be comparable to divided dose therapy in acute mania. Hence, single dose lithium should be preferred in the management of acute mania, in order to improve compliance and in view of the other potential benefits discussed above.

REFERENCES

Amdisen, A. (1975) Sustained release preparations of lithium. In *Lithium Research and Therapy,* (Ed F.N.Johnson). Orlando: Academic

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition revised. Washington DC: American Psychiatric Association.

Bramble, D. (1992) A survey of lithium use in the elderly. *International Journal of Geriatric Psychiatry,* 7, 819-826.

Grof, P., MacCrimmon, D.J. & Smith, E.K.M. (1980) Long-term lithium treatment and the kidney. *Canadian Journal of Psychiatry,* 25, 535-543.

Jensen, H.V., Olafsson, K., Bille, A., Andersen, J., Mellerup, E.T. & Plenge, P. (1990) Lithium every second day. A new treatment regimen? *Lithium,* 1, 55-58.

Kehoe, R.F. & Mander, A.J. (1992) Lithium treatment prescribing and monitoring habits in hospital and general practice. *British Medical Journal,* 304, 552-554.

Lauritsen, B.J., Mellerup, E.T., Plenge, P., Rasmussen, S., Vestergaard, P. & Schou, M. (1981) Serum lithium concentration around the clock with different treatment regimens and diurnal variation of renal lithium clearance. *Acta Psychiatrica Scandinavica,* 64, 314-319.

Muir, A., Davidson, R., Silverstone, T., Dawnay, A. & Forsling, M.L.(1989) Two regimens of lithium prophylaxis and renal function. *Acta Psychiatrica Scandinavica,* 80, 579-583.

Perry, P.J., Dunner, F.J., Hahn, R.L., Tsuang, M.T. & Berg, M.J. (1981) Lithium kinetics in single daily dosing. *Acta Psychiatrica Scandinavica,* 64, 281-294.

Plenge, P. & Mellerup, E.T. (1986) Lithium and the kidney. Is one daily dose better than two? *Comprehensive Psychiatry*, 27, 336-342.

Schou, M., Amdisen, A., Thomsen, K., Vesterguard, P., Iletmar, O., Mellerup, E.T., Plenge, P. & Rafaelsen, O.J. (1982) Lithium treatment regimen and renal water handling. The significance of dosage pattern and tablet type examined through comparison of results from two clinics with different treatment regimens. *Psychopharmacology*, 77, 387-390.

K.P.Suresh DPM, Research Medical Officer; K.M.R.Prasad MD, DNB (Psy), Senior Resident; Rajesh Mohan DPM, Research Medical Officer; M.V.Ashok MD, Senior Resident (Formerly); S.K.Chaturvedi MD, Additional Professor; K.N.Sreenivas MD, Additional Professor (Retd), Department of Psychiatry; Chittaranjan Andrade MD, Associate Professor, Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore 560 029.*

* Correspondence: No.8, Type IV, NIMHANS Quarters, Byrasandra, Jayanagar, Bangalore 560 011.