Indian J. Psychiat., 1997, 39 (3), 232-238

LOXAPINE IN THE TREATMENT OF SCHIZOPHRENIA : AN OPEN STUDY

S.A. EMMANUEL, H.NAIDU & V.B. SOVANI

ABSTRACT

Sixty six patients of either sex with a diagnosis of schizophrenia as per DSM III-R criteria were enrolled in an open, non-comparative study. They were treated with loxapine over a duration of 6 weeks. The assessment of the patients was carried out using the Positive and Negative Syndrome Scale (PANSS) and Clinical global Impression (CGI) Scale. The side effects were noted on the Extrapyramidal Rating Scale and Asberg Scale for side effects. There was a statistically significant improvement in all the item scores of PANSS except 'Guilt Feeling' and 'Depression'. A similar significant improvement was also observed in the factor scores and cluster scores of PANSS. On analysis there was substantial improvement in the negative scale ratings on PANSS in the negative subtyped group (13 sub). The average dose of loxapine received by patients at the time of completion of the study was 96.75±36 mg per day. The most commonly reported side effects were dryness of mouth, constipation & drowsiness. Loxapine appeared to be effective and well tolerated in the treatment of acute exacerbation in schizophrenia. Evaluation of loxapine in the treatment of negative symptoms of schizophrenia merits particular attention.

Key words : Loxapine, schizophrenia, negative symptoms

Loxapine is a neuroleptic of the dibenzoxazepine class. The pharmacological profile includes blockade of 5-HT, dopaminergic and histamine receptors, but the muscarinic and receptor blockades are weak, (Vanelle et al., 1994).

Loxapine closely resembles the other traditional antipsychotics in its therapeutic efficacy and side effects profile. It has been mainly used as an 'antiproductive' drug with better response in patients with paranoid schizophrenia. It has been effective in treating acute as well as chronic cases of schizophrenia (Heel et al., 1978; Ayd, 1977).

In the studies on loxapine published earlier including those conducted in India (Seth et al., 1979; Malik et al., 1980; Bagadia et al., 1980; Dube and Kumar, 1976), the standard scales such as Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression Scale (CGI) & Nurses, Observation Scale for Inpatient Evaluation (NOSIE) have been used for evaluation of the patients. However, it has been suggested that Loxapine actions justify further studies using better targeted scales such as PANSS (Positive and Negative Syndrome Scale) considering the deficit reduction suspected in the initial stages (Vanelle et al., 1994).

MATERIAL & METHOD

PANSS was initially formulated in the early eighties as a special adaptation of two psychiatric rating instruments -BPRS & psychopathology rating schedule. Later it was modified, expanded and standardised with

greater psychometric sophistication for positive/ negative evaluation. It consists of positive scale (7 items measuring symptoms that are superadded to a normal mental status), negative scale (7 items assessing features absent from a normal mental status), composite scale (based on the differential between positive and negative scales to specify the degree of preponderance of one syndrome over the other) & a general psychopathology scale (16 items assessing overall severity of the schizophrenic disorder) (Kay et al., 1986). This is a comprehensive scale that measures not only general and somatic symptoms but also focuses on the positive and negative aspects of the disease.

The CGI was used to asses overall improvement in the clinical condition. For measuring the side effects of the drug & the extent of extrapyramidal symptoms, the Asberg scale & the Extrapyramidal Symptoms Rating Scale were used.

66 patients of either sex between 18 and 60 years of age diagnosed to have exacerbation of schizophrenia as per DSM III R criteria were enrolled in a 6 week open, non comparative study conducted at Nur Manzil Psychiatric Centre, Lucknow. These included both new cases as well as acute exacerbation of chronic schizophrenia. Patients with following characteristics were excluded from the study: known hypersensitivity to dibenzoxazepine derivatives; severe hepatic, renal, cardiovascular, endocrine or other neurologic diseases including mental retardation; treatment with psychotropic or other antipsychotic drugs 24 hours prior to the start of the study; patients below 18 years and above 60 years of age and pregnant and lactating women.

Following enrolment, the patients were rated on the PANSS & the CGI scales by an independent observer unaware of the treatment to be given. The patients were then hospitalized.

The treatment was started with loxapine at a dose of 25 mg twice a day and rapidly increased with increments every week to the effects and tolerated dose. The upper limit of 250 mg for the daily dose was not exceeded in any patient. Concomitant use of psychotropic drugs was not allowed. Antiparkinsonian drugs

TABLE 1
CHANGE IN THE MEAN SYNDROME SCORES AND CLUSTER SCORES OVER THE DURATION OF STUDY

Syndrome/cluster scores	Basal	Week 1	Week 2	Week 4	Week 6
Positive synd. score	26.31	23.83**	19.19**	14.17**	11.24**
Negative synd. score	18.80	17.31**	15.51**	13.81**	11.41**
General psychopathology score	40.85	37.31**	31.79**	26.13**	22.78**
Anergia	9.61	8.92**	8.11**	6.83***	6.22**
Thought disturbance	14.17	13.38**	11.21**	8.72**	6.81**
Activation	7.61	6.73**	5.96**	4.67**	3.85**
Paranoid belligerence	11.41	9.90**	7.57**	5.59**	4.43**
Depression	6.48	6.13	5.91*	5.69*	5.50**

* $p < 0.05$ ** < 0.01
Friedmann two way ANOVA followed by multiple comparison tests

TABLE 2
MEAN PERCENTAGE MAXIMUM POSSIBLE CHANGE FROM BASELINE FOR SYNDROME SCORES & CLUSTER SCORES

Sr. No.	Syndrome/Cluster	Change from baseline (%)			
		Week 1	Week 2	Week 4	Week 6
1	Positive Syndrome	14	38	66	80
2	Negative Syndrome	19	25	36	51
3	general Psychopathology	16	38	61	73
4	Anergia	17	28	46	60
5	Thought disturbance	9	33	58	75
6	Activation	20	40	67	83
7	Paranoid Belligerence	17	45	70	83
8	Depression	9	27	30	45

were permitted in the event of extrapyramidal side effects. Other drugs indicated for the treatment of concurrent physical diseases arising during the trial period were allowed. A record of all such medications was maintained. The patients were assessed at the end of 1,2,4 & 6 weeks using the rating scales mentioned above.

The study completed at the end of 6 weeks unless terminated earlier due to serious adverse or toxic effect related to treatment.

The individual item scores and factor scores assessed by using the rating scales at baseline and the subsequent evaluation were analysed by ANOVA, Friedmann two way followed by multiple comparisons.

RESULTS

Out of the sixty six patients enrolled, fifty four patients completed the study successfully and were considered for analysis.

There were 6 cases of protocol isolations, like use of additional antipsychotics (5 cases) or ECT (1 case). There were 5 dropouts (4 for logistical reasons and 1 due to unsatisfactory response). One case had to be withdrawn due to extrapyramidal side effects. This case has been included in the analysis of side effects.

The demographic profile of the 54 analyzable patients is as follows : the number of female patients completing the study was 23 (42.6%) and that of male patients was 31(57.4%). The mean age of patients was 29.5 years (s.d. 10.7 years). There were 23 patients (42.6%) with diagnosis of paranoid schizophrenia, 13(24.1%) with disorganised schizophrenia, 10 (18.5%) with undifferentiated schizophrenia and 8 (14.8%) with catatonic schizophrenia . 15 patients were new cases, 27 patients had one or two previous attacks of the disease, while 12 patients had 3 to 6 attacks in the past.

The change in the individual item rating scores of the positive scale, the negative scale and the general psychopathology scale in PANSS showed that for all the item except guilt feelings, tension, anxiety and depression, there was a statistically significant improvement. It was apparent in many item from week one itself (17 out of 28 items) and in most by the end of 2 weeks (25 out of 28 items).

Amongst the positive symptoms-delusions, hallucinations, suspiciousness,

TABLE 3
MEAN PERCENTAGE MAXIMUM POSSIBLE CHANGE FROM BASELINE FOR NEGATIVE SCALE ITEMS IN PATIENTS WITH NEGATIVE SUBTYPE OR MIXED TYPE OF DISEASES

Sr. No.	Item	No. of patients	Change from baseline (%)			
			Week 1	Week 2	Week 4	Week 6
1	Blunted affect	12	7	19	36	48
2	Emotional withdrawal	15	15	26	40	48
3	Poor Rapport	16	18	42	61	69
4	Passive/apathetic social withdrawal	14	16	36	46	55
5	Difficulty in abstract thinking	18	10	28	43	64
6	Lack of spontaneity & flow of conversation	15	21	44	69	85
7	Stereotyped thinking	7	31	44	91	91

hostility & unco-operativeness improved by the end of the first week, while conceptual disorganisation, unusual thought content improved by the second week. All negative items improved by the first week except social withdrawal, motor retardation and social avoidance that improved by second week.

It was however, noticed that the mean initial score for each item was less than 4 in most cases (4 in PANSS indicates a moderate severity)., The inference was that pooling of various cases had masked the score. Hence syndromes and clusters were analysed.

Analysis of the syndrome scores i.e. positive syndrome, negative syndrome, and general psychopathology also showed a highly significant improvement from week one and was continued till the end of the study period. A similar picture emerged from the analysis of cluster scores namely anergia, thought disturbance, activation, paranoid belligerence and depression. Table 1 summarizes the change in syndrome scores and cluster scores.

To get a better idea of the real change, the mean percentage maximum possible improvement was calculated (table II). It was then noted that improvement for all syndromes and cluster at 6 weeks was more than 60% except for negative syndrome (51%) and depression (45%). On a closer look at the data it was noted that although few patients had a high score for some negative items, the mean initial score for pooled patients was two, suggesting mild disease. Hence, we tried to study cases with a predominance of negative symptoms separately.

The PANSS scale gives two methods of identifying negative subtypes of schizophrenia. A quantitative measure indicated by negative composite scores. This measure identified 13 cases. Another is a count of positive and negative items. At least three moderate ratings on the negative scale and less than three on positive scale indicates negative schizophrenia, while three or more than three moderate scores on both scales indicate : mixed type (8). This measure identified 6 cases of mixed schizophrenia with a predominance of negative symptoms.

The diagnoses in these 19 patients were as follows: disorganised schizophrenia (9) undifferentiated schizophrenia (6), paranoid schizophrenia (3) and catatonic schizophrenia (1). Analysis of the percentage maximum

possible change from baseline (table III) for the items of negative scale in these patients revealed a marked improvement by the end of the study.

There was a significant improvement in the severity of illness on Clinical Global Impression Scale ($p<0.001$) .

Side effects were recorded both on Asberg's Side Effects Scale and the extrapyramidal rating scale. General side effects as per Asberg's Scale are listed in Table IV. Dry mouth, drowsiness, constipation, fatigue were most common, but of mild to moderate severity.

The common extrapyramidal effects noted were : tremor, rigidity, akathesia and diminution of facial expression (table V). There were 70 events in 31 patients. Of these 24 cases had to be administered benzhexol in a dose of 2 to 6 mg/day. The case that was withdrawn due to side effects has been included in this analysis.

The average daily dose of loxapine used during the study period was 54.15±12.5 mg (baseline), 81.6±16.21 mg (wk1) 97.68±25.58 mg (wk2), 105 133.8 mg (wk4) and 96.75±36 mg (wk6).

TABLE 4
SIDE EFFECTS GENERAL (ASBERG SCALE) (N=56)

Side effects	No. of patients
Physical tiredness	4
Sleeping disturbance	3
Headache	1
Dizziness	1
Orthostatic hypotension	5
Palpitations	3
Tremor	10
Perspiration	1
Dryness of mouth	17
Constipation	4
Micturition disturbance	1
Drowsiness	8
Sexual dysfunction	1
Total Events in 33 cases	59

TABLE 5
SIDE EFFECTS : EXTRA PRAMIDAL SYMPTOMS (N=56)

Extrapyramidal symptoms	No. of Patients
Facial expression	5
Dysarthria	4
Rigidity (neck)	5
Rigidity (arm)	8
Tremor (face and head)	5
Tremor (arms)	19
Tremor (legs)	3
Gait	5
Posture	6
Akathesia	9
Total events	70
No. of patients with EPS	31

The concomitant medications used during the study were as follows: benzhexol hydrochloride (dose range 2 to 6 mg/day, 24 patients), nitrazepam (5 to 10 mg/day, 4 patients), lorazepam (1 to 2 mg/day, 2 patients) & imipramine (75 mg/day; 1 patient).

DISCUSSION

Schizophrenia has been recognised as a complex disease marked by various symptoms affecting aspects of human cognition, emotion and behaviour. Bleuler, who coined the term 'Schizophrenia' proposed a conceptual division of symptoms into 'accessory' (unstable florid symptoms) and 'fundamental' (more permanent breakdowns in mental function). Other terms that have been used include 'productive/deficit or positive/negative' symptoms (Mortimer & Mckenna, 1992).

Although recognised as early as the beginning of this century, the research interest in negative symptoms was overshadowed by the weightage given to the positive symptoms.

The interest in negative symptoms was renewed in the late seventies and early eighties resulting in the realization that the negative

symptoms were ubiquitious in nature, excess morbidity was associated with them, and they were generally not responsive to pharmacological therapy.

The last of these observations has spurred a lot of research activity into the efficacy of antipsychotics in treating the negative symptoms (Miller et al., 1994). Development of newer psychiatric rating instruments such as PANSS, has also helped to standardise the positive-negative evaluation.

Earlier studies on loxapine did not use scales that addressed positive and negative symptoms, hence PANSS was used in this study.

In our study marked improvement was seen in most items, syndrome and cluster scores by first week. This speed of response is in keeping with various other studies, (Serban, 1997), some of which demonstrated an effect even within 48 hours (Moriarty et al., 1979; Zisook & Click, 1980).

Dose used was gradually increased from 50 mg to 150 mg. The mean dose used at the end of the study was 96.75 mg, indicating a slight reduction in dose after the fourth week. Such a reduction has been recommended, and the maintenance dose in expected to be between 60 and 100 mg (Ayd, 1977). Malik & Kumar (1980) in their study also required a mean dose of 91.5 mg.

Loxapine is known for its action on paranoid schizophrenia (Vanelle et al., 1994; Heel et al., 1978; Ayd, 1977). In the present study it showed excellent response in positive symptoms.

On closer scrutiny there were only 19 cases with a predominance of negative symptoms, a number too small for meaningful statistical analysis. When these cases were analysed item wise on a percentage maximum possible improvement basis an impressive improvement was seen in all negative items.

Most of the side effects were of mild to moderate severity, with only one dropout due to adverse reactions. Ayd (1977) mentions that clinically it is difficult to predict who will respond to loxapine and who will not, a fact borne out by the two cases who were withdrawn from the study due to an unsatisfactory response.

These observations indicate that loxapine certainly deserves further evaluation in the treatment of negative symptoms of schizophrenia. Trivedi & Aga (1994) have earlier recommended that diphenylbutyl priperidines such as pimozide or penfluridol with their calcium channel antagonism should be tried in negative symptoms; and Venelle et al. (1994) recommends clozapine or risperidone. The possibility that loxapine which is an established, effective and safe neuroleptic may emerge as a viable alternative for management of negative symptoms needs to be further investigated.

REFERENCES

Ayd, F.J. (1977) Loxapine update: 1966-1976. *Dis. Nerv., Syst.*, 38, 883-887.

Bagadia, V.N., Shah, L.P., Abhyankar, R.R. (1980) A double blind controlled trial of loxapine and trifluoperazine in adolescent schizophrenia. *Curr. Ther. Res.*, 27, 386-396.

Dube, K.C. & Kumar, N. (1976) Loxapine succinate: a comparative study with chlorpromazine. *Curr. Ther. Res.*, 19, 653-659.

Heel, R.C., Brogden, R.N., Speight T.M. & Avery G.S. (1978) Loxapine-a review of its pharmacological properties and therapeutic efficacy as an antipsychotic agent. *Drugs*, 15, 198-217.

Kay, S.R., Opler, L.A. & Fiszabin, A. (1986) Positive and negative syndrome scale (PANSS), *Rating Manual*, 1-63.

Malik, S.C. & Kumar, K. (1980) Loxapine in adolescent Schizophrenia : a comparative study with trifluoperazine . *Curr. Ther., Res.*, 28, 432-446.

Miller, D.D., Flaum, M. & Arndt, S. (1994) Effect of antipsychotic withdrawal on negative symptoms in schizophrenia. *Neuropsychopharmacology*, 11, 11-20.

Moriarty, D.M., Berger, J.R. & McGarth, S.A. (1979) Loxapine succinate in acute schizophrenia outpatient in a day care setting. *Curr. Ther.,*

Res., 26, 408-414.

Mortimer, A. & Mckenna, P.J. (1992) Negative symptoms of schizophrenia. *Practitioner*, 236, 255-260.

Serban, G. (1979) Loxapine in acute schizophrenia disorder. *Curr. Ther., Res.*, 25, 139-143.

Seth, S., Mahal, A.S. & Kumar , K.A. (1979) A double-blind comparative trial of loxapine & trifluperazine in chronic schizophrenic patients. *Curr. Ther., Res.*, 25, 320-329.

Trivedi, J.K. & Aga, V.M. (1994) What is the current status of pharmacotherapy for negative symptoms of schizophrenia. *Archives Of Indian Psychiatry*, 1, 144-148.

Vanelle, J.M., Olie, J.P. & Levy-Soussan, P. (1994). New antipsychotics in schizophrenia, the French experience. *Acta Psychiatrica Scandinavica*, 89 (Suppl 380), 59-63.

Zisook, S. & Click, M.A. (1980) Evaluation of loxapine succinate in the ambulatory treatment of acute schizophrenic episodes. *International Pharmacopsychiatry*. 15, 365-378.

S.A. EMMANUEL, M.D, DPM., Director , Consultant Psychiatrist , H.NAIDU, DPM., Consultant Psychiatrist, Nur Manzil Psychiatric Centre, Lalbagh, Lucknow-226001. V.B., SOVANI, Medical Director, Cyanamid India Limited, Mumbai - 400025.*

Correspondence