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A prospective study of clozapine in treatment-resistant schizophrenic patients

I. Preliminary report

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Abstract. Preliminary results of a non-blinded prospective study of the effect of clozapine on symptomatology and social function in 51 treatment-resistant schizophrenic patients are reported. The mean duration of treatment at the time of this report was 10.3 ± 8.1 months, median 7.6 months. Overall, 3/51 patients (60.8%) showed at least a 20% decrease in total BPRS, a criterion of improvement in the study of Kane et al. (1988). Four of 51 (7.8%) had at least a 50% decrease in total BPRS. Improvements in both positive and negative symptoms were noted. Marked improvements in social function were noted within the first 6 months of treatment. Improvement was first noted at all time points, with only 45.2% of improvers being identified after 6 weeks of treatment. These results suggest a 6–12-month trial may be desirable before deciding to discontinue clozapine because of insufficient response. Higher total Brief Psychiatric Rating Scale (BPRS) score and higher ratings on the Paranoid Disturbance subscales of the BPRS were factors which discriminated clozapine responders from non-responders.

Key words: Clozapine – Treatment-resistant schizophrenia – Quality of life

Clozapine has been reported to be superior to chlorpromazine in a 6-week double-blind study of 268 proven neuroleptic-resistant chronic schizophrenic patients (Kane et al. 1988). Altogether, 30% of the clozapine-treated schizophrenic patients responded according to predetermined criteria which included a minimum 20% decrease in total score on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1960) as well as other criteria (Kane et al. 1988). Examination of the week-by-week ratings of change in total BPRS score indicated that the rate of change, i.e., the slope of the change in BPRS total score over time, had not significantly diminished by 6 weeks, suggesting that further improvement might be expected had the controlled observation period continued beyond 6 weeks. There have been no prospective studies of the clinical response to clozapine over longer periods in treatment-resistant schizophrenic patients. Three retrospective reports of clinical response to clozapine from Scandinavia in treatment-resistant schizophrenic patients have found that between 33 and 51% of a total of 289 chronic schizophrenic patients treated with clozapine alone had a good response over treatment intervals ranging from a month to more than 12 years (Juul-Povlsen et al. 1985; Kuha and Meittenen 1986; Lindström 1988). These studies did not examine the time of onset of response. Kuha and Meittenen (1986) reported that age, sex, dose or duration of illness or hospitalization did not predict response to clozapine.

Because the use of clozapine carries with it the risk of agranulocytosis in 1–2% of cases (Krupp 1989), it is highly desirable to target the patient population in whom it is most likely to be effective so that all such patients receive an adequate trial with the drug. Similarly, knowledge of the duration of treatment with clozapine in which clinical response is most likely to be achieved is important to avoid continuing treatment with clozapine after the time when the likelihood of the first appearance of significant benefit is small in relation to the risk of granulocytopenia. This will be discussed in more detail subsequently.

Another critical issue with regard to clozapine which needs consideration is the effect of clozapine treatment on the quality of life. The concept of quality of life is an attempt to assess aspects of the social function of schizophrenic patients beyond hospitalization and psychopathology (Lehman 1983). As measured by the scale of Heinrichs et al. (1984), this includes the ability of the chronic schizophrenic patient to achieve competence and satisfaction through close relationships with family and friends, to participate in and enjoy social activities, to take initiative, to work, take care of family or go to school, to have a sense of purpose and motivation, to experience pleasure and utilize time carefully, etc. Lindström (1988) reported that 39% of the clozapine-treated patients in his study were working within 2 years of initiating treatment with clozapine, compared to less than 2% in the year prior to clozapine. In the 6-week multicenter study of hospitalized treatment-resistant patients by Kane et al. (1988), improvement in ward behavior and social interaction was noted. Other than these data, we are aware of no other information indicating whether the improvement in psychopathology consequent to clozapine treatment has a significant effect upon the quality of life of the treatment-resistant schizophrenic patient.

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Methods

Fifty-one schizophrenic patients who met DSM-III criteria for schizophrenia were included in this open study of treatment-resistant schizophrenics. Thirty seven of 51 (72.6%) patients were hospitalized at University Hospitals of Cleveland; 13/51 (25.5%) were hospitalized at the Cleveland Veterans Administration Hospital. One patient was begun on clozapine as an outpatient. The mean age of the patients was 35.5±SD 7.3 years; age of onset was 20.0±6.7 years. There were 34 males and 17 females. The number of previous hospitalizations was 8.4±6.8. The total BPRS scale score at baseline was 51.5±SD 11.8 The length of hospitalization after starting clozapine was 48.7±46.5 days. After discharge, University Hospital patients were seen in a weekly clinic in which they received additional supportive group and family therapy. The VA outpatients received group therapy.

Diagnoses were based on interviews of the patient using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978) supplemented with additional questions from the Present State Examination (Wing 1974) which facilitate making DSM-III diagnoses. All diagnoses were made by consensus of a research psychiatrist and other research and clinical personnel who collected the primary clinical data, which also included a review of all data available from previous admissions. Patients had to have failed to respond to at least two trials of two different neuroleptic drugs of different classes. These trials had to be at usually adequate dosages (i.e., ≥800 mg chlorpromazine/day) for at least 4 weeks each. Most of the patients had had many more than two unsuccessful drug trials. Lack of response to neuroleptic treatment was indicated by persistent moderate-severe delusions, hallucinations or thinking disorders which were disturbing to the patient and interfered with social function, rather than a specific total BPRS score, which was a requirement of the study of Kane et al. (1988). All patients gave written informed consent to be included in the study.

Psychopathology was assessed by means of the BPRS, as well as other rating scales. Only the BPRS data will be reported here. The BPRS was ascertained prior to beginning treatment with clozapine, and after 6, 13, 26, 39, 52, 65, and 78 weeks of treatment. Some ratings were missed at specific periods. In addition, ratings made within 4 weeks before or after the later scheduled time period were included in a few instances. The Quality of Life scale (QLS; Heinrichs et al. 1984) was used to assess the effect of clozapine treatment on social function. These ratings were made by direct interview of patient and a family member whenever possible. As this part of the study was initiated after the trial was begun, some initial QLS ratings were obtained by a retrospective interview of the patient and family.

Drug treatment. Clozapine was initiated at a dose of 25 mg/day and increased at a rate of 25 mg/day unless cardiovascular effects intervened. After achieving a dose of 175 mg/day, it was usually possible to increase the dose by 50 mg increments. The dose was increased until side effects were noted or, on the basis of clinical judgement, it was felt that the dosage was optimal. The maximum dose was 900 mg/day. Drug administration was usually twice per day. Occasional doses of lorazepam were permitted to decrease anxiety or facilitate sleep.

Other treatments. After discharge, all patients and their families participated in group therapy which focused on social skills and functioning outside of the hospital.

Data analysis. The data was analysed by *t*-test, analysis of variance and analysis of covariance.

Results

Fifty-one patients who completed at least 6 weeks of treatment are included in this report. The longest duration was 35.2 months; mean=10.3±SD 8.1 months; median, 7.6 months. Thirty-eight of the 51 (74.5%) patients were still receiving clozapine at the time of this report. Others dropped out for the following reasons: 1) failure to respond ($N=2$); 2) non-compliance ($N=5$); 3) agranulocytosis ($N=1$); 4) cardiovascular side effects ($N=5$). The mean dose of clozapine was 502±SD 232/mg/day, median 500 mg.

Total BPRS scores for all time periods are given in Fig. 1. There was a significant decrease in BPRS at 6 weeks and at all subsequent time periods compared to baseline. It can be seen that the major decrease in mean BPRS occurred during the first 6 weeks but that mean BPRS declined at each of the subsequent time periods. Because this is an initial report of an ongoing study with no fixed duration, the number of subjects decreased inversely with the length of observations. There were significant differences in the total BPRS scores between 6 weeks and 9 and 12 months but not between 6 weeks and 3 or 6 months (data not presented). Similarly, the total BPRS score was significantly lower at 9 and 12 months but not 6 months, compared to 3 months. The number of subjects was only 11 in the longest comparison. There were no significant differences between 6 and 9 months but there was a significant improvement between 6 and 12 months ($N=9$, $P=0.03$) and a trend between 9 and 12 months ($N=11$, $P=0.08$). The change in total BPRS was clearly smaller during the latter periods. Thus, the mean change in total BPRS was 9.3±10.6 between baseline and 6 weeks ($N=40$, $P=0.0001$), only 2.5±13.4 between 6 weeks and 3 months ($N=40$, $P=0.05$) and 3.2±11.2 between 3 months and 6 months ($N=26$, $P=$NS).

We also observed significant decreases in the BPRS subscales Paranoid Depression and Withdrawal/Retardation (Fig. 2). The rate and extent of improvement was not significantly different. To investigate the relationship be-

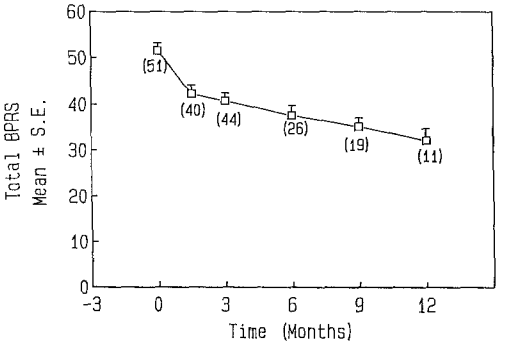

Fig. 1. Total Brief Psychiatric Rating Scale scores in clozapine-treated patients over a 12-month period. Mean±SEM (N=number of patients)

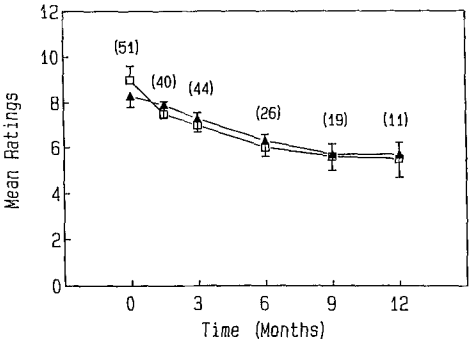

Fig. 2. Paranoid Disturbance and Withdrawal Retardation subscales of Brief Psychiatric Rating Scale in clozapine-treated patients over a 12-month period. Mean±SEM (N=number of patients) □ Paranoid disturbance; ▲ withdrawal retardation

Table 1. Effect of covarying change in positive symptoms from change in negative symptoms

Time	N	Unadjusted mean	Adjusted mean
Initial	26	8.31	8.09
6 months	26	6.31	6.52*

Overall model: $F=4.34$; $df=1,51$; $P=0.0003$

* $P=0.05$

Table 2. Initial and final BPRS scores in responders

Group	BPRS		
	Initial	Final	Δ
≥20% decrease	54.7±4.5	35.7±11.3	19.0±10.8
≥50% decrease	63.6±10.4	30.3±3.3	33.3±6.3

Table 3. Time at first appearance of 20% or 50% decrease in total BPRS score

Time	20% decrease			50% decrease		
	N	% Subjects[a]	% Improvers[b]	N	% Subjects	% Improvers
6 weeks	14	27.5	45.2	1	2.0	25.0
3 months	9	17.6	29.0	1	2.0	25.0
6 months	2	3.9	6.5	2	3.9	50.0
9 months	5	9.8	16.5	0	–	–
12 months	1	2.0	3.2	0	–	–
Total	31		100	4		100

[a] of all 51 subjects
[b] of improvers

tween improvement in positive and negative symptoms, we conducted and analysis of covariance in which the final ratings for Withdrawal/Retardation are adjusted for initial Withdrawal/Retardation, and initial and final ratings of the BPRS positive symptom items (Thinking Disturbance plus Suspiciousness). As can be seen in Table 1, there was still significant improvement in the Withdrawal/Retardation factor, indicating that the improvement in negative symptoms was independent of the improvement in positive symptoms.

Thirty-one of the 38 (81.5%) patients who remained on clozapine (60.1% of the initial 51 entered) achieved at least a 20% decrease in total BPRS score. Four of the 38 (10.5%) achieved at least a 50% decrease. The initial and final BPRS scores of these subjects are presented in Table 2. The mean decrease in BPRS in the group of 31 responders was 33.0%. We next examined when patients first showed at least a 20% or 50% decrease in total BPRS compared to baseline (Table 3). It may be seen that some patients showed their initial period of improvement at each time period. There was a substantial (17.6%) proportion of patients who first improved at 13 weeks. Two patients first showed at least a 20% decrease in total BPRS score after 12 months, following 9 months with a lesser change.

Two of the 51 patients (19%) required rehospitalization for psychiatric reasons. This occurred after 3 and 4 months of treatment. In one instance, it was due to non-compliance with clozapine. Reinstitution of clozapine again produced improvement in symptomatology. The other remained a non-responder but has still had clozapine for only 7 months. One patient who was a good responder to clozapine developed a granulocytosis. After it was stopped, she relapsed within 3 weeks. She failed to respond over the next 15 months to two typical neuroleptic drugs, including loxapine, a chemical congener of clozapine.

Quality of life

Quality of Life ratings for the total scale score and selected items scores for 33 patients are given in Table 4. Significant improvement was, in fact, noted in all 21 items. When we divided the patients on the basis of duration of observation by a median split, the change in total Quality of Life ratings noted in the 16 patients with the shorter period of observation (3.0±2.1 months) was 22.4±28.3 months, which was not significantly different from that in the 17 patients (32.0±16.4, P=NS) with a longer observation period (16.0±7.8 months).

Predictors of response

We next examined differences in demographic and psychopathological features in patients who improved at least 20%. Total BPRS scores and ratings of the Paranoid Disturbance Subscale and the Thinking Disturbance Subscale (trend) were the factors which discriminated responders in univariate analysis (Table 5). Higher total BPRS score and higher Paranoid Disturbance and Thinking Disturbance scores were characteristic of responders. Responders were younger than non-responders, but this difference was not significant. There was no significant difference in pretreatment Quality of Life total scores and ventricular brain ratios as determined by CT scan (data not presented) in the responders and non-responders.

Discussion

This study provides the first prospective quantitative data on the results of clozapine treatment in treatment-resistant schizophrenic patients. The limitations of this study must be noted at the outset. The sample size is relatively small, and 4/51 (7.8%) of the patients had been studied for only

Table 4. Effect of clozaril treatment on quality of life ($N=33$)

	Pre-treatment	Post-treatment	P
Total scale score	25.4 ±18.6	53.0±24.0	0.0001
Intimate relations	1.9 ± 1.4	3.5± 1.6	0.0001
Social activity	1.1 ± 1.2	2.1± 1.5	0.003
Social initiative	0.9 ± 1.2	2.0± 1.8	0.004
Social withdrawal	1.3 ± 1.1	2.8± 1.3	0.0001
Occupation function	0.75± 1.7	1.7± 1.8	0.003
Motivation	1.0 ± 1.5	2.7± 1.9	0.0002
Anhedonia	1.2 ± 1.1	1.9± 1.5	0.0001
Time utilization	0.98± 1.3	2.5± 1.9	0.0001

Table 5. Comparison of responders[a] and non-responders

	Responders[a] (31)	Non-responders (20)
Age (years)	33.4± 7.2	36.0± 7.4
Age of onset (years)	20.3± 7.3	19.8± 5.8
Total BPRS	54.7±10.3	46.5±12.5*
BPRS Paranoid Dist.	10.0± 4.1	7.4± 4.4*
BPRS Thinking Dist.	11.8± 4.5	9.8± 3.9**
BPRS Withdrawal/Retard.	8.6± 3.5	7.9± 4.3
Quality of Life total	22.1±15.9	25.2±14.2

[a] Patients with at least a 20% decrease in total BPRS

* Difference between responders and non-responders is significant with $P<0.05$; ** $p=0.10$

6 weeks and 17/51 (33.3%) for only 13 weeks at the time of this analysis. Nevertheless, the mean duration of the treatment period (10.3 months) was far greater than that of any other prospective study. Secondly, treatment was on an open basis and there was no comparison treatment (In future, we will report on a follow-up of 19 patients who were accepted for inclusion in this study but who refused to take clozapine or who could not tolerate clozapine.) Finally, only historical criteria were used to determine whether patients were responders or non-responders at the time of entry. However, although the patients in this study did not have a prospective trial with another typical neuroleptic drug to demonstrate non-responsiveness, all had been receiving a typical neuroleptic just prior to beginning treatment with clozapine and were still highly symptomatic.

With these limitaions in mind, the following observations can be made. The total BPRS in this sample prior to treatment was slightly lower than that in the Kane et al. (1988) study after adjustment for the 1–7 rating system in that study. However, the number of hospitalizations was the same in this group as was the age of the patients. There were significantly more females in this group. However, we found no difference in response to clozapine in males and females. The magnitude of the improvement in total BPRS in the first 6 weeks of clozapine treatment: 17.1±18.0%, $N=40$, is some what smaller than the 25% decrease in the study of Kane et al. (1988). However, the percentage of patients who responded at 6 weeks with at least a 20% decrease in total BPRS score was some what higher in this study (45.2% vs 30.0%). Thus, the results of this study might be construed as a confirmation and extension of the results in the 6-week study of Kane et al. (1988), since the patient groups appear comparable. Patients included in this study should be representative of the type of treatment-resistant schizophrenic likely to be eligible for clozapine treatment in the United States, should it be approved by the US Food and Drug Administration as a drug for treatment-resistant schizophrenics.

A key issue left over from the study of Kane et al. (1988) was clinical change after 6 weeks of treatment. The total BPRS scores in this group continued to decrease after 6 weeks of treatment. This finding is consistent with the prediction that could be made from the data of Kane et al. (1988). Because the number of subjects in this study was relatively small (only 19 with at least 9 months treatment), it would be premature to conclude at what point maximal response to clozapine is achieved. What is most noteworthy is the clear evidence that the majority of the patients who improved at least 20% by total BPRS criteria did so for the first time after 6 weeks. By 3 months, 23/31 (74%) of the responders at the 20% criterion and had been identified. All responders were identified by 12 months. The available data suggests that at least 6 months and perhaps as much as 12 months of clozapine treatment is warranted before concluding that a patient is a non-responder to clozapine. Of course, no one criterion such as percentage of change in total BPRS is a sufficient measure of clinical response. Since 80% of cases of a granulocytosis develop 18 weeks of clozapine treatment (Krupp 1989), the decreased risk of a granulocytosis after 4–5 months of treatment diminishes the risk/benefit ratio of a more prolonged trial with clozapine in a patient who shows no improvement after 3–6 months of treatment. This issue needs re-examination with a large cohort of patients who have had at least 12 months of clozapine treatment.

The finding that patients tended to be younger at the time of treatment with clozapine responded better has potential implication for how clozapine should be used. If supposed, by further data, it suggests that clozapine treatment might be most advantageous when started early in the course of chronic schizophrenia. Whether the benefit to be gained from early treatment with clozapine warrants the increased risk of usually reversible a granulocytosis will require much further investigation to determine if this is the case, it will be necessary to it mount a prospective long term trial of clozapine treatment in neuroleptic-responsive patients to determine what effect this might have on the course of illness. There is some evidence from controlled trials that clozapine is superior to chlorpromazine in neuroleptic-responsive schizophrenic patients (Claghorn et al. 1988). Thus, it is possible that the outcome of schizophrenia might be more favorable were schizophrenic patients to be treated with clozapine after the second episode (as opposed to the mean of eight episodes in this study and that of Kane et al. (1988).

The improvement in the Quality of Life scale (Heinrichs et al. 1984) ratings reflected what was very evident from clinical work with these patients. Marked increases in interest in activities and social interaction began early in the treatment process and often seem to exceed what might be expected on the basis of improvement in psychotic symptomatology alone. Improvement in negative symptoms was independent of change in positive symptoms and the clozapine-treated patients; thus differs from our findings with chronic schizophrenic patients who are not treatment resistant and who were treated with typical neuroleptic drugs

(Meltzer et al., in preparation). In conjunction with supportive group and family therapy, and some limited skills training, some patients were able to make notable improvement. This included being able to work as a volunteer, hold a job or return to school. Twenty of the 38 patients improved in these categories. A number of patients achieved independent or semi-independent living status compared to chronic hospitalization prior to beginning clozapine.

In conclusion, clozapine treatment proved very effective in the majority of these treatment resistant patients. The improvement was noted in symptomatology as well as Quality of Life. Improvement occurred within 6 weeks in less than half of those who responded. Therefore, a treatment trial should run for longer than this, at least 6–12 months in our judgement. Patients who had a higher total BPRS and were more paranoid were better responders to clozapine.

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