AN OPEN CLINICAL TRIAL WITH CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENICS

A. K. AGARWAL, MUKUL SHARMA, SHRIKANT SRIVASTAVA, MRINAL MULLICK & ASHUTOSH KUMAR

ABSTRACT

In an open trial, drug-resistant schizophrenics were treated with clozapine for sixteen weeks. The patients were rated on BPRS, PANS, Side effects scale and Global Impression Scale at weeks 0, 9 and 16. A battery of base-line investigations were done, and hemogram was repeated at weekly intervals. Of the total 29 patients included, 25 completed the trial. The patients showed significant improvement on both BPRS and PANS, although the improvement was more in initial weeks than between 9 and 16 weeks. The most common side effects observed were sedation, hypersalivation and tachycardia. Issues of response of clozapine on negative symptoms and a longer duration of the drug therapy are discussed.

Keywords: clozapine, open trial, treatment-resistant schizophrenia

Clozapine is an atypical antipsychotic with superior efficacy in severely ill, treatment-resistant schizophrenics. It is a noncataleptic agent (Coward et al., 1990) with high affinity for D, and D, receptors (Van Tol et al., 1991), besides having action on 5TH, (Altar et al., 1988) and 5TH, sites (Canton et al., 1990).

Its efficacy in schizophrenia was clearly demonstrated in earlier studies (Elholm & Haggerstrom, 1974; Singer & Law, 1974; Fischler Cornilson & Ferner, 1976) but it was withdrawn from the market following reports of associated agranulocytosis (Tidlamp-Hiikkle et al., 1977), a potentially life-threatening side-effect.

It was not until late eighties, that Kane et al. (1988) demonstrated the usefulness of clozapine in severely ill treatment resistant schizophrenics. This led to rejuvenation of interest in the drug, and many studies, both of controlled (Pickar et al., 1992); and descriptive type (Meltzer et al., 1999; Davies et al., 1991; Wilson, 1992) were published. These studies gave clozapine a solid standing in the treatment of schizophrenic patients who were resistant to conventional neuroleptics.

With clozapine being prescribed more frequently, although not regularly to every schizophrenic patient, further issues opened up. One such point of debate was its ability to ameliorate negative symptoms. The drug was seen to have an unequivocal effective response on positive symptoms, and some studies also reported improvement in the negative symptoms. But what was not clear in these studies was whether or not the secondary negative symptoms that responded. As these studies also reported diminution in positive and extrapyramidal symptoms, this possibly could have led to a secondary improvement in the negative symptoms, rather than being a direct action of the drug. Addressing this issue, Brier et al. (1994) in a double blind study of clozapine and haloperidol concluded that the former drug was comparatively superior in treating negative symptoms, although this effect was relatively minor. However, as haloperidol itself is known to have propensity for producing extrapyramidal symptoms, this conclusion does not seem to be very convincing. Other studies that support its efficacy in ameliorating the negative symptoms have also been published (Meltzer et al., 1989; Pickler et al., 1992; Clozapine Study Group, 1993; Miller et al., 1994) while others have refuted this finding (Brier et al., 1994; Conley et al., 1994). Carpenter et al. (1995) are profoundly committed to the idea that the deficit state is enduring and that no treatment yet available can provide effective relief.
Thus the present study was undertaken to evaluate the efficacy of clozapine in an open trial in schizophrenic patients who were non-responsive to the classical antipsychotics.

**MATERIAL AND METHOD**

In an open, non-comparative and non-cross-over study schizophrenics were taken up for a 16 week trial. The cases selected were either chronic schizophrenics, acutely relapsed schizophrenics, or chronic schizophrenics with exacerbation. The diagnosis of schizophrenia was made according to ICD-10 (WHO. 1992). All the patients had already been treated in vain with at least two neuroleptics chosen from chlorpromazine (1000 mg/day or more), haloperidol or trifluoperazine in dose equivalents of 1000 mg/day or more of chlorpromazine. These drugs had already been tried for a period of at least six weeks in the past.

All the patients were rated on the following instruments by one of the authors (MS)

1. Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham. 1962) at weeks 0, 9, and 16.
2. Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1988) at weeks 0, 9, and 16.
3. Global Impression Scale at the beginning and end of the trial.
4. Side-effects scale-weekly.
5. Blood cell counts (Hb, TLC, DLC) - once weekly during the trial period and until 4 weeks later.
6. Blood pressure, pulse and temperature were recorded at weekly intervals.

All the patients were given a washout period of one week who were on oral neuroleptics, and four weeks for depot preparations. The patients who were not receiving any neuroleptics at the time of intake in the trial were initiated on clozapine right away after baseline investigations were completed. The initial dose was 50 mg/day which was increased to 100 mg/day by the end of the first week. Increments were made in the dose as 100 mg/week to achieve a daily dose of 300 mg by the end of the fourth week. From fifth to sixteenth week the dose range was 300-450 mg/day depending upon the therapeutic response and/or the presence of side effects.

The permitted concomitant medication was oral trihexyphenidyl for extrapyramidal symptoms, and nitrazepam for sleep.

Baseline investigations comprised of SGOT, SGPT, ECG, serum creatinine, chest X-ray, complete hemogram and urine analysis.

A total leucocyte count below 3500/cmm or granulocyte count below 1500/cmm warranted cessation of clozapine therapy.

The total scores of BPRS and subscales of PANSS were compared at 9 and 16 weeks from the baseline. Paired 't' test was employed to compare these ratings. The side-effect scores were calculated as the total percentage of patients exhibiting them.

**RESULTS**

A total of 29 patients, between the ages 18-40 years, were included in the study, of which 4 dropped out for various reasons (seizures -1, GIT disturbance -1, pyrexia -1 and intercurrent illness-1). Thus 25 patients (18 males and 7 females) completed the study. The mean age of the patients and the duration of illness were 28.8±5.2 years and 7.3±4.2 years respectively.

**TABLE 1**

| BPRS TOTAL SCORES | MEAN | S.D |
|--------------------|------|-----|
| Week 0             | 40.76| 12.50|
| Week 9             | 27.72| 7.74*|
| Week 16            | 23.20| 5.11**|

*Paired t-value = 17.53, d.f. = 24. (p<.001)
**Paired t-value = 22.30, d.f. = 24. (p<.001)

The BPRS scores (Table1), when compared from week 0 (40.8±12.5) showed improvement both at week 9 (27.7±7.7) and week 16 (23.2±5.1), which was highly significant statistically.

The improvement on BPRS total scores is further illustrated by the observation that by the end of 9th week, of the 25 patients, 17(68%) had shown improvement upto 25%. By the end of trial i.e. 16 weeks, the number had changed to 19(76%) in the 26-50% group and 6(24%) in the 0-25% group. None
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TABLE 2
PERCENTAGE IMPROVEMENT FROM BASELINE TOTAL SCORES

| PERCENTAGE IMPROVEMENT | 9TH WEEK | 16TH WEEK |
|------------------------|----------|-----------|
| 0-25                   | 8 (32%)  | 6 (24%)   |
| 26-50                  | 17 (68%) | 19 (76%)  |
| Above 50               | Nil      | Nil       |

of the patients had improved beyond 50% as compared to the baseline (Table 2).

The PANSS scores also showed similar improvement, but the results were more variegated. When compared from the baseline, at week 9 the scores for the positive and negative syndromes, and general psychopathology showed moderately significant improvement (p<0.05) (Table 3), while for

TABLE 3
SCORES ON PANSS SUBSCALES

| MEASURES      | WEEK 0 MEAN (S.D.) | WEEK 9 MEAN (S.D.) | WEEK 16 MEAN (S.D.) |
|---------------|--------------------|--------------------|---------------------|
| Positive      | 19.08 (6.82)       | 13.68 (4.80)*      | 10.38 (3.87)        |
| Syndrome     | 20.08 (5.91)       | 13.80 (5.77)*      | 12.36 (6.01)        |
| Negative      | -0.28 (5.36)       | 0.08 (5.72)        | -2.24 (4.87)        |
| Syndrome     | 36.20 (10.1)       | 25.64 (8.30)       | 22.28 (5.97)*       |
| Composite Index |                 |                    |                     |
| General Psychopathology |  |                    |                     |

For all values d.f. = 24; *p<0.001

TABLE 4
SCORES ON PANSS MEASURES

| MEASURES      | WEEK 0 MEAN (S.D.) | WEEK 9 MEAN (S.D.) | WEEK 16 MEAN (S.D.) |
|---------------|--------------------|--------------------|---------------------|
| Anergia       | 10.8 (3.34)        | 6.52 (2.21)**      | 6.16 (2.57)**       |
| Thought       | 11.8 (3.57)        | 8.84 (3.39)**      | 6.64 (3.34)**       |
| Disturbance   | 4.92 (2.17)        | 3.88 (1.42)**      | 3.64(1.26)**        |
| Activation    | 9.00 (3.76)        | 5.8 (2.49)**       | 4.2 (1.49)**        |
| Paranoid/Belligerence | 7.36 (4.13) | 5.60 (2.26)** | 4.92 (1.83)*       |

for all values d.f.=24

*p<0.05, **p<0.01, ***p<0.001

anergia, thought disturbance and paranoid/belligerence showed highly significant improvement (p<0.001) (Table 4); for the rest of the subscales, the scores were significant at p<0.01 level.

At week 16, the trend for improvement on PANSS continued, but with little variation. Compared to that at week 9, for the positive syndrome, negative syndrome, general psychopathology, anergia, thought disturbance and paranoid/belligerence the improvement was similar, but that in activation was much more (p<0.01), and for depression much less (p<0.01), as compared to the other variables.

The side-effect profile (Table 5) shows that the most frequently observed side-effect was tachycardia throughout the period of the trial (68% at week 1, 48% at week 9, and 60% at week 16), followed by mild hypersalivation (40%, 48% and 28% respectively). Although a general trend seen was in diminution in the frequency of the observed side-effects, but sedation (mild) showed an acclivity with the progression of the trial. Moderate sedation was maximally observed in the initial week, and severe
sedation, although present initially in only a few
patients (16% at week 1), gradually diminished in
frequency (8% and 4% at weeks 9 and 16 respec-
tively).

A significant finding was that among the 4
dropouts, none were due to hematological side-effec-
t.

DISCUSSION

Ours was an open study in which the efficacy
of clozapine was evaluated in patients of schizophre-
nia who had been labeled previously as chronic/resis-
tant or were intolerant to conventional
neuroleptics.

In our study the initial BPRS scores were quite
high, and showed a steady diminution over the du-
ration of the trial. The improvement rated between
weeks 9 and 16 was much more than that in the ini-
tial nine weeks. However, as the trial was terminated
at this point, it cannot be commented whether this
improvement would have accrued further or achieved
a plateau. Other studies of longer duration have re-
ported that the benefits stabilize in about 3-6 months
time, after which no further benefit is seen
(Lindstrom. 1988 ; Meltzer, 1992 ; Brier et al., 1993).
However, this time course of improvement seems not
unique to clozapine, as Carpenter and colleagues
(1995) have commented that a similar response time
course is seen with the standard neuroleptic treat-
ment.

In our study, clozapine was found to be effec-
tive against positive and negative symptoms both,
as measured on PANSS. The changes in the nega-
tive symptoms, when compared from the baseline,
were highly significant (Table 4), and the patients
showed benefit on all the parameters. Other workers
have shown a differential response on negative symp-
toms.

While Kane et al. (1988) found that clozapine
significantly reduced scores for emotional with-
drawal, blunted affect and psychomotor retardation,
Meltzer et al. (1989) have reported that affective flat-
tening and anhedonia does not respond to the drug.
It has also been shown in some studies that the pri-
mary negative symptoms do not respond to clozapine
(Conley et al., 1994), but the drug is only of use in
ameliorating the secondary negative symptoms. Brier
et al. (1994) in a controlled study, found that the
patients with primary negative symptoms responded
poorly to clozapine, although it was beneficial in
patients with non-deficit schizophrenia. In our study
we did not differentiate between deficit and non-defi-
cit schizophrenia, neither covaried the significance
of response in negative symptoms to the positive
symptoms.

Clozapine, initially introduced about 3 decades
ago, was withdrawn from the market owing to re-
ports of agranulocytosis induced by it. Lieberman et
al. (1988) have cited a 2% cumulative incidence af-
ter 52 weeks of clozapine treatment for
agranulocytosis. In our study none of the patients
developed even leucopenia sufficient enough to stop
the treatment.

The other common side-effects observed in our
study were sedation, hypersalivation, tachycardia,
postural hypotension and dizziness (Table 5). Fitton
& Heel (1990) have observed similar side-effects in
as many as 40% of their of their patients. Brier et al.
(1994) also found excessive salivation and
tachycardia to be most frequently observed adverse
effect, which is in close agreement with our find-
ings.

This being one of the first studies in the coun-
try, we do not have other data to compare our find-
ings with the patients in this country. This initial
study has shown the benefits of clozapine in chronic
or treatment-resistant patients which argues favor-
ably for the drug. As it is a new drug for this coun-
try, and consequently, there not being much clinical
experience with it, the clinicians should be cautious
in using it.

ACKNOWLEDGEMENT

We acknowledge with thanks M/s Sun Phar-
maceuticals Industries Ltd. for providing Clozapine.

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