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AN OPEN STUDY OF CLOZAPINE IN THE TREATMENT OF RESISTANT SCHIZOPHRENIA

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ABSTRACT

This open study was undertaken to assess the efficacy of clozapine in resistant schizophrenics, its side effects and safety profile and the mean dose required. Sample consisted of 28 patients who had been previously treated with neuroleptics and ECTs. A special proforma was prepared for recording the psychopathology and side effect profile. The complete blood count, differential count and BPRS scores were recorded weekly for a period of 3 months. Within 1 month of treatment on a dose range of 100-200 mg/day, a 25%-50% decline in the BPRS score was noticed. the mean dose required was 241 mg/day. Sedation and sialorrhoea constituted the commonest side effects in 90% patients. No case of agranulocytosis was reported. The implications of the study are discussed.

Key words : Clozapine, treatment resistant schizophrenia

The introduction of typical neuroleptic agents in 1950 was a dramatic advance to treat patients with schizophrenia. Despite this a deterioration in the level of functioning and associated side-effects of neuroleptics still continue to be a problem in many schizophrenics. A relapse rate of 15-20% also occurs every year (Kane et al.,1988). Clozapine has been recommended in patients who are resistant to or intolerant of typical neuroleptics. According to Kane (1992) and Meltzer (1992), failure to respond to atleast two and/or three typical neuroleptics given for atleast 6 weeks each, should be considered as treatment resistant schizophrenia.

The most exciting current development is the re-emergence of clozapine as a highly effective atypical antipsychotic drug for the treatment of resistant schizophrenics. Clozapine is a dibenzodiazepine with pharmacological and therapeutic profile that distinguishes it from classical antipsychotics like phenothiazines, butyrophenones, diphenyl butylpiperidines and thioxanthines. In contrast to these later groups, clozapine by virtue of its chemical structure exerts a weak antagonism at central dopamine D_2 receptors and more pronounced inhibition of dopamine D_1 mediated activation of adenylate cyclase and potent blockade of central serotonergic, adrenergic and cholinergic receptors (Kaplan & Saddock,1996). More over, clozapine is only marginally effective in several animal behavioural models (e.g. induction of catalepsy and suppression of dopamine induced stereotypy).

Early enthusiasm about the drug was marred by recognition in 1970, that it caused agranulocytosis. Only recently a sufficiently compelling data has been gathered that clozapine can be used safely if special surveillance is undertaken to monitor its potentially severe toxic effects (Anderman & Griffith,1997). In our search for better treatment options for resistant schizophrenia, clozapine has definitely provided a ray of hope. The present study was undertaken to study the (1) efficacy

of clozapine (2) side effects and safety profile of clozapine and (3) mean effective dose required for the Indian setting.

MATERIAL AND METHOD

In an open and non-comparative study, the sample consisted of randomly selected 28 patients who were attending the outpatients department of psychiatry, of a general municipal hospital. All the patients satisfied the DSM-IV criteria for schizophrenia (APA,1994). They were either chronic or acutely relapsed schizophrenics or those who were prone for the extra pyramidal side effects of potent neuroleptics. These patients were previously treated for a minimum of eight weeks with at least two neuroleptics viz, chlorpromazine (1000 mg/day or more), haloperidol or trifluoperazine in dose equivalents of 1000 mg/day of chlorpromazine and a course of 6-10 ECTs. None of the patients were on long term depot preparations.

As they were found to be treatment resistant, they were taken up for the study. Patients having comorbidity of affective disorders, substance use disorders or organic dysfunction were excluded from the study. After taking informed consent, the history was recorded as per the specially prepared proforma. Baseline investigations viz. complete haemogram, chest X-ray, SGOT, SGPT, ECG, serum creatinine and urine analysis were done before starting clozapine. The psychopathology, side-effect profile with the blood cell counts (TLC & DLC) and the dose of clozapine were recorded weekly. Brief Psychiatric Rating Scale (BPRS, Overall & Gorham,1962) was used to rate the psychopathology weekly.

All the patients in this study were followed over a minimum period of three months to evaluate their improvement. Before the initiation of clozapine therapy a wash out period of 7 days was given to those patients who were on oral neuroleptics. Patients who were on a drug holiday or had relapsed after stopping neuroleptics were started on clozapine after doing the baseline investigations. The initial dose of clozapine was 25 mg/day which was increased to 100 mg/day by the end of two weeks. Then the doses were titrated accordingly with increments being made by 25-50 mg every week. The gradual titration was done to see the therapeutic response to the minimum dose of clozapine and/or the presence of side effects with the maximum dose range being 425-525 mg/day by the end of three months. The side effects were recorded weekly and the scores were calculated at the end of 3 months as the total percentage of patients exhibiting them. A watch was kept for a decrease in the leucocyte count below 3000/cu mm or in the granulocyte count below 1500/cu mm which would necessitate discontinuation of clozapine. The total BPRS scores were compared at the end of 1 and 3 months respectively from the baseline score with the help of the paired t-test and the percentage improvement in the BPRS score at the end of three months was noted.

RESULTS

The population under study consisted of 28 patients, with age ranging from 15 to 60 years and a mean age of 32.64±13.73 years. There were 13 males (46.43) and 15 females (53.57%). Most of the patients were from low or lower middle socio-economic class with poor educational background.

TABLE 1
BPRS TOTAL SCORES

	MEAN	S.D.
Baseline	29.75	9.49
After 1 month	19.70	8.10 *
After 3 months	14.71	7.08 **

* Paired 't' value = 4.34; d.f.=27; (p<0.005)
** Paired 't' value = 8.89 ; d.f.=27; (p<0.005)

The BPRS scores when compared from baseline (29.75±9.49) showed improvement both at the end of one month (19.7±8.1) and three months (14.71±7.08), which was statistically significant.

When the percentage improvement in the BPRS scores at the end of 3 months was assessed, it was found that of 28 patients, 14

TABLE 2
PERCENTAGE IMPROVEMENT ON BPRS TOTAL SCORES FROM BASELINE

Percentage Improvement	After 3 months (N=28)
0 - 25	3 (10.71%)
26 - 50	14 (50.00%)
51 - 75	10 (35.72%)
76 & above	1 (3.57%)

(50%) had shown improvement in the range 26-50%, with 10(35.72%) patients having improvement in the range of 51-75% whereas only 3(10.71%) patients did not show improvement beyond 25% from the baseline.

TABLE 3
SIDE EFFECT PROFILE OF CLOZAPINE OVER 3 MONTHS

Symptoms	Total No. of Patients (n=28)
Sedation	26 (92.85%)
Sialorrhoea	26 (92.85%)
Dizziness	16 (57.14%)
Constipation	14 (50.00%)
Hypotension	11 (42.85%)
Weight gain	11 (42.85%)
Tachycardia	5 (17.85%)
G.I. Upset	4 (14.28%)
Anticholinergic effects	2 (7.14%)
Fainting Spells	2 (7.14%)
Myoclonus	---
Seizures	---
Agranulocytosis	---

The side effects profile revealed sedation and sialorrhoea to be the most frequently observed side effects in 26(92.85%) patients. Hypotension and weight gain were seen in 11 (42.85%) patients.

A significant finding was that none of the patients developed agranulocytosis. The regular monitoring of the blood count towards the end of 3 months, revealed an increase in the count in 7(25%) patients, though it was not above 13,000/cu mm and a decrease in 4(14.28%) patients but not below 4,000/cu mm.

The mean dose of clozapine in our study was 241 mg/day. As evident from the table, only 6(21.45%) patients required doses more than 325 mg/day by the end of 3 months. 9(32.13%) patients were receiving clozapine in the range 226-325 mg/day, 8 (28.57%) patients responded

TABLE 4
DOSE OF CLOZAPINE

Dose Range (mg/day)	At 3 Months Total No. of Patients (n=28)
25 - 125	5 (17.85%)
126 - 225	8 (28.57%)
226 - 325	9 (32.13%)
326 - 425	4 (14.30%)
426 - 525	2 (7.15%)

to clozapine in the range 126-225 mg/day whereas, 5(17.85%) patients were maintained on doses between 25-125 mg/day.

DISCUSSION

Clozapine has found to result in moderate to marked overall symptomatic improvement in approximately 60-80% of patients with acute or chronic schizophrenia. Marked improvement consistently occurred in symptoms of hallucinations, hostility and thought disorders (Klik,1976; Lapierre,1980). This finding was also seen in our study where many of the positive symptoms of schizophrenia responded earlier when rated on the BPRS. As we had not used the Positive and Negative Syndrome Scale (Kay et al.,1988), we could not comment on those patients having associated negative symptoms or their improvement in comparison to the positive symptoms in our study.

Though clozapine is more propagated for the negative symptoms of schizophrenia, it definitely improves the positive symptoms much earlier in treatment resistant schizophrenics (Kane,1988). Meltzer et al.(1989) reported that affective flattening and anhedonia did not respond to clozapine. Studies by Conley et al. (1994) and Brier et al.(1994) also suggest that the drug helps only in ameliorating the secondary negative symptoms rather than the primary negative symptoms. Kane (1993) also reported a pronounced anxiolytic effect within 1-2 weeks of clozapine therapy, before the onset of its antipsychotic action.

A 50-75% decrease in the total BPRS score with clozapine was seen in 35.72% of our patients by the end of 3 months. However, previous studies revealed only a 20%

improvement in 40-60% of patients over a period of 1.5 to 6 months (Lindstrom,1988; Meltzer et al.1989; Mattes,1989; Brier et al.,1993). These studies also reported that the benefits occurred in the early phase of treatment and stabilised in the initial 3-6 months after which, no further benefit was seen. It also remains to be seen whether the patients in our study would have shown further improvement or reached a plateau as the study was terminated at this point.

Clozapine became unpopular due to its dangerous side effect of agranulocytosis, which is reversible in early stages with a maximum risk being in the first 18 weeks of treatment (Anderman,1977; Andrew & Rennie,1990). Fortunately, none of our patients developed this potentially dangerous side effect. Lieberman et al.(1988) cited a 2% cumulative incidence after 52 weeks of clozapine treatment for agranulocytosis. However, benign leucocytosis can occur in the initial stages, which was also seen in our study (Kaplan et al.,1996). Sedation, sialorrhoea, dizziness and hypotension were the most commonly seen side effects in our patients, a fact which was also reported in previous studies (Fitton & Heel,1990; Brier et al.,1994). 42% of our patients complained of weight gain, keeping in with the study by Umbricht et al. (1994). Most of these low dose side effects are associated with clozapine titration and tend to lessen and disappear when dosage reaches 300-400 mg/day. However, we did not notice much diminution in the frequency of the observed side effects during our study period.

The data on the dose range of clozapine revealed a lower mean dose of 241 mg/day, in the Indian population as per our study which was similar to the trial conducted in Europe where the mean dose was 283 mg/day. However, studies in the US revealed higher mean dose of 444 mg/day though the response rate was strikingly similar (Fleischhacker,1994). This finding is significant because if patients can be maintained on a lower dose then the toxic side-effects can be avoided.

In conclusion, this trial was conducted to study the efficacy of clozapine in treatment resistant schizophrenics does propagate the benefits of the drug. It also reveals that there are no dangerous side effects of the drug except for sedation and sialorrhoea which may decrease with clozapine titration. The required mean dose in our study was much less than in the western counter parts. Though the study sample was small and screened over 3 months, a larger sample with an adequate time span would be more fruitful in yielding the shortcomings of the present study.

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