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Initial Experience with Clozapine in Woodbridge Hospital

K E Wong, S A Chong, F Ngui, M Winslow, G S Devan, O K Leong, C H L Choo

ABSTRACT

Objectives: This study was performed to evaluate the efficacy and side-effect profile of the atypical neuroleptic clozapine in local Asian patients with treatment-resistant schizophrenia.

Method: Patients were treated with 12 weeks of clozapine after undergoing a washout of all previous neuroleptics. They were assessed weekly on the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) and the Simpson-Angus Scale for Extrapyramidal Side-Effects.

Results: Clinical improvement (according to criteria established a priori) at study end point was shown in 78.9% of the patients. There was no statistical difference in the incidence of the extrapyramidal side-effects at starting and end points. The mean daily dosage was 356.6 mg. The most common adverse effect was hypersalivation.

Conclusion: Clozapine is effective and well tolerated in local patients with treatment-resistant schizophrenia.

Keywords: clozapine, schizophrenia, efficacy, Asian

INTRODUCTION

Schizophrenia is the most severe of all mental disorders that affects about 1% of the population. It is characterised by the presence of positive symptoms (eg. hallucinations and delusions), negative symptoms (eg. affective flattening, avolition and anhedonia), and disorganisation[1,2]. These disturbances usually result in chronic social and occupational impairment[3,4]. The mainstay of treatment is classical neuroleptics such as chlorpromazine, trifluperazine, and haloperidol among which none has emerged substantially superior over the rest. These compounds cause extrapyramidal symptoms (EPS) and are ineffective in about 30% of patients[5]. They are also relatively ineffective for negative symptoms[6]. Since the discovery of chlorpromazine in the 1950s, no significant advances were made in the treatment of schizophrenia until the advent of clozapine, an atypical neuroleptic.

Clozapine is associated with few or no acute EPS nor tardive dyskinesia[7]. Belonging to the class of dibenzodiazepines, it was first introduced as an anti-psychotic drug in Europe in the late 1960s. In 1975 however, 16 patients in Finland developed agranulocytosis, 8 of whom died later from secondary infection[8]. This led to its withdrawal in most countries until its revival in a study by Kane et al[9] in America which demonstrated its efficacy in the treatment of refractory schizophrenia. Clozapine became available in Singapore in 1993.

The aim of this study was to evaluate the efficacy and side-effect of clozapine in the local Asian context.

METHODS

All patients met the DSM III-R criteria for schizophrenia. Treatment refractory patients were defined as those who had received at least two 6-week periods of treatment during the preceding 5 years with at least two chemically different anti-psychotics at doses equivalent to at least 600 mg/day of chlorpromazine without substantial relief of symptoms. Subjects had to be between 18 and 60 years of age, without significant medical illnesses, and had to undergo a washout period (one week for oral anti-psychotics and two weeks for depot injection). Severity of psychopathology for inclusion was a Brief Psychiatric Rating Scale (BPRS)[10] total score exceeding 40 performed at baseline (18-item version, in which 1 indicates "absent", and 7 indicates "severe"). Written informed consents were obtained for all subjects.

Patients were started with clozapine 12.5 mg/day and titrated to 300 mg/day over 3 weeks. If significant improvement was shown at any dosage below 300 mg/day, that dosage was maintained. Further increase beyond 300 mg/day depended on the patient's clinical response.

Patients were assessed weekly with the BPRS and Clinical Global Impression (CGI)[11]. Adverse reactions were evaluated by systematic patient query and observation. Systematic assessments were made weekly using the Simpson-Angus Scale for Extrapyramidal Side-Effects[12]. Weekly full blood counts were done and urea/electrolytes, liver function tests and electrocardiograms were done at baseline, week 6 and 12. Subjects were dichotomised as responders or non-responders according to the criteria of Kane et al[9], where response was at least 20% decrease in the total BPRS score from baseline and must attain either a BPRS total score of 34 or less, or a CGI of 3 or less. Characteristics and clinical ratings were compared with Wilcoxon signed-ranks test.

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Table I - Characteristics of 19 patients treated with clozapine for 12 weeks

Patients (N=19)	BPRS			CGI			Simpson-Angus Scale			Dosage (mg/day)	
	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12	Week 6	Week 12
Responders at week 12											
1	43	24	22	5	4	3	0	0	0	300	300
2	57	22	23	7	4	4	0	0	0	300	350
3	40	31	26	6	6	3	0	3	1	300	400
4	52	34	34	7	6	5	1	1	0	225	425
5	41	22	21	6	3	3	0	0	0	375	450
6	40	24	23	4	3	3	0	0	0	200	200
7	52	34	32	5	4	4	0	0	1	300	300
8	48	31	32	6	4	4	2	0	3	300	300
9	44	35	24	6	4	3	1	1	1	250	300
10	45	35	20	5	4	3	1	1	1	275	300
11	44	38	28	6	4	4	4	2	1	275	275
12	47	39	32	6	6	5	1	0	0	375	350
13	55	36	33	6	4	4	7	1	1	300	300
14	45	36	30	5	4	3	1	1	1	400	500
15	44	38	28	6	4	4	4	2	1	275	275
Non-responders at week 12											
16	44	34	36	4	3	4	2	0	1	300	400
17	48	36	37	5	5	5	1	1	0	300	450
18	51	37	36	7	4	4	1	1	0	400	500
19	71	41	36	7	4	4	0	0	1	300	400
Mean	48.0	33.0	29.1*	5.7	4.2	3.7*	1.4	0.7	0.7	302.6	356.6
SD	7.4	5.9	5.7	0.9	0.9	0.8	1.9	0.9	0.8	53.3	83.68

* $p < 0.05$ vs values at baseline (Wilcoxon's test)

RESULTS

There were 15 Chinese, 3 Malay and 1 Indian patients, 13 of whom were women. The mean age of the 19 patients was 32 years (range, 24 to 40 years). The mean duration of illness was 15 years (range, 5 to 24 years), with a mean age of onset of illness at 17 years (range, 12 to 25 years). The mean dose of clozapine for the 19 patients at the end of the 12-week period was 356.6 mg/day (range, 200 to 400 mg/day). Table I shows the data of all 19 patients classified as responders and non-responders. Fifteen (78.9%) of the patients showed a positive response at the end of the study period.

There was no significant change in the EPS as assessed by the Simpson-Angus Scale at both the baseline and end-point of the study. The most common side-effect was hypersalivation which occurred in 13 patients (66%). Sedation occurred in 9 patients (47%). Four patients (21%) had weight gain. Three patients had tachycardia. One patient had seizure at a dose of 300 mg/day of clozapine. No patient developed any blood dyscrasia, and three patients had transient mild elevations of their liver enzymes.

DISCUSSION

Our response rate of 78.9% is higher than that reported in other studies of 30% to 61%[9,12]. The mean dose of 356.6 mg/day lies between the mean doses in European studies (283.7 mg/day) and (444 mg/day) in American studies[13]. The higher mean daily dose of the American studies has been suggested to be due to patients selection where the patients were more chronically ill and had a more restrictive definition of treatment resistance as the criteria for inclusion in the studies[13]. Our patients were more similar in these aspects to the subjects in the American studies.

This study found no significant difference in extrapyramidal side-effects before and after twelve weeks of treatment which is expected, as one of the advantage that clozapine has over the typical neuroleptics is the low incidence of extrapyramidal side-effects. The other side-effects reported are similar to those reported in the US and European studies[13] where the most common side effects were hypersalivation and sedation. None of the 19 patients developed any blood dyscrasia. The risk of agranulocytosis remains the most serious and

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Our results showed the efficacy of clozapine in the treatment of refractory schizophrenia. However, this study is limited by the small sample size, the open design study which might inflate the response rate, and the lack of assessment over a longer treatment duration. For patients with treatment-resistant schizophrenia, clozapine is an important therapeutic advancement but the risk of agranulocytosis and seizures, and the cost of clozapine in comparison to that of typical neuroleptics requires close monitoring and optimisation of its use.

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