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Full Length Research Paper

Comparison between clozapine, an atypical antipsychotic agent and haloperidol, a conventional agent used to treat schizophrenia

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An observational and comparative study was conducted to compare the functional outcome between the patients treated with conventional antipsychotic agent haloperidol and atypical antipsychotic agent Clozapine (clozaril) . A total of 32 patients were included in the study with established schizophrenia according to (DSM iv). The data was processed on SSPE 10th version. The primary outcome measure was the improvement of negative symptoms of schizophrenia and secondary outcome measure was to observe the superiority of the atypical drug Clozapine over conventional agent haloperidol regarding side effects. Patients were assessed at baseline, 2nd and 8th week, using four tools of assessment. For treatment group receiving haloperidol mean was 47.2 ± 11.50 at 8th week and for Clozapine treatment group mean was 38.0 ± 15.39. The P values for all the parameters in the Clozapine group were significant as compared to haloperidol.

Key words: Clozapine, haloperidol, schizophrenia, dopamine receptors, antipsychotic agents.

INTRODUCTION

The terms antipsychotic, neuroleptic or major tranquilizer are applied to drugs that are used in the treatment of psychosis beneficial. They have effects on mood and thought, but carry the risk of producing side effects that mimic neurological diseases (Citrome et al., 2001). The limitations of conventional antipsychotic have prompted a search for new agent with greater efficacy (particularly against negative symptoms) and fewer side effects. One promising strategy has been to investigate agent that block both dopamine and serotonin receptors. The role of serotonin in schizophrenia has been proposed in 1954 (Woolley and Shaw, 1954). The newer atypical antipsychotic have the neuropharmacological properties of being effective against emotional with drawl and other negative symptoms of schizophrenia with clear efficacy compared with agents against positive symptoms of delusion. The antipsychotic drugs had great impact in the treatment of psychosis in general and schizophrenia in particular. Newer or atypical antipsychotic drugs include Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone and Amisulphride. These antipsychotic have become the most commonly employed agents for the treatment of psychotic disorders in many countries (Bladessarini and Tarzai, 1996). The term “Atypical” has been used to designate there relative freedom from risks of adverse extra pyramidal syndromes (EPS) including akathesia, dystonia, parkinsonism and Tradive Dyskinesia (TD) or tradive dystonia, compared with older, potent anitidopaminergic type antipsychotic.

The advent of atypical antipsychotic has revolutionized the treatment of psychosis in the elderly. The general psychiatric literature indicates that the atypical agents are as efficacious in reducing positive symptoms as the conventional agents; more efficacious against negative

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symptoms, and to have a much more benign adverse effect profile (Andreason, 1985) . The currently marketed atypical agents are cloazpine, risperidone, Olanzapine and quetiapine. These drugs are available in the US and UK and a number of other countries worldwide. The essential feature of an atypical antipsychotic is less acute extra pyramidal symptoms, especially dystonia associated with therapy as compared with a typical antipsychotic like haloperidol.

Clozapine is useful in treating acute, chronic and refractory schizophrenic patients. Clozapine is best known atypical antipsychotic (Ackenheil, 1989; Barnes and McPhillips, 1998). Preclinical animal testing shows that it blocks apomorphine or amphetamine-induced hyperactivity, but does not produce catalepsy except at high doses (Barnes, 1999). It is the first antipsychotic that demonstrated a significant effect on negative symptoms, as well as reducing anxiety and tension (Andearson, 1990). Clozapine exerts its main antipsychotic action by blockede of limbic DA receptors (Baldessarini and Frankenburg, 1996).

It also improves cognition and smooth pursuit eye movements. Its clinical efficacy is thought to be associated with is interactions with both dopaminergic and serotonergic neurotransmitter system (Pickar et al., 1994). Clozapine has been shown to be effective than congenital neurolptic drugs in reducing both the positive and negative symptoms of schizophrenia (Wahlbeck et al., 1999), being effective in around 60% of all patients with treatment-resistant disease (Meltzer, 1990).

The present study was designed to compare the functional outcomes between patients of schizphrenia receiving a conventional antipsychotic agent, haloperidol and an atypical agent, Clozapine.

MATERIALS AND METHODS

This is an observational and comparative study conducted on patients suffering from schizophrenia. The duration of study was 8 weeks; sampling was done through systematic randomization. All selected patients were divided into four groups, having eight patients in each group using a conventional agent and an atypical agent.

Inclusion criteria

Patients fulfilling the criteria of (DSM iv) having schizophrenia according to international classification of diseases.

Exclusion criteria

Patients having concomitant physical morbidity along with schizophrenia

The primary purpose of this study was to determine if Clozapine was superior to Haloperidol in improving overall psychopathology. The analysis was done on intent-to-teat basis. The patient entered in the study was assessed at baseline, for 2 weeks and data were processed on SSPE 10th version, adequately tabulated and statistical analysis was done.

Drugs and dosage

Following drugs and corresponding doses were used:

1.) Haloperidol (Trade name; Serenace) dose = 50 - 60 mg in divided doses.
2.) Clozapine (Trade name; Clozaril) dose = 100 - 60 mg in divided doses) (not to be given more then 320 mg because of side effects.

Instruments

Brief Psychiatric Rating Scale (BPRS). This instrument has 16 items each scored on a seven points scale. For example, absent, minimal, mild, moderate, moderate-severe, severe, and extreme. The items include anxiety, emotional withdrawal (autism), depressive mood, guilt feeling etc. There are criteria to define the symptomatology items but not the severity ratings. It is suitable for rating of sever psychiatric illness but not minor disorders.

Positive and negative syndrome rating scale (PANSS)

This scale rates blunted effect, poor rapport, social withdraw difficulty in abstract and stereo typed thinking and lack of spontaneity. A thirty minutes interview is required. It has seven items for positive symptoms and seven items for negative symptom and scoring is the same as in BPRS.

Extra pyramidal symptom rating scale (EPSRS)

On which quantitative rating of the symptoms of parkinsnism, dystoniaand dyskinesia is done. It has twelve items each scored on four points scale.

Quality of life questionnaire (WHO QOL-BREF)

Quality of life is a general term applied to the totality of physical, psychological and social functioning. It is determined by physical impairment, emotional reaction, personality, illness etc. QOL scale requires great deal of concentration and responsibility and assessed very carefully as involves many diverse aspects and is laborious. It has 26 items each scored on five-point scale. Increase in total count means an improvement in the symptoms and hence in the quality of life.

DISCUSSION

The currently popular term “Atypical” was introduce to differentiate the antipsychotic from the classic or “Typical” antipsychotic (narcoleptics) (Annabel et al., 1991) defined atypical antipsychotic as drug with 1.) decreased or absent acute EPS and tardive dyskinesia: 2.) increased symptoms; and 3.) decreased or absent capacity to elevate prolactin (Bustillo et al., 1996). The concept of atypical antipsychotic is equivocal and still changing with the development of new compounds and discovery of their clinical features. Further to the hetero drugs and the difficulty of establishing a common definition the term “Atypical” should be replaced by “Novel” antipsychotic. But this term is also not precise. However, an important part of the definition must be the low or absent liability for producing EPS (Kane et al., 1994).

The negative symptoms of schizophrenia included the spectrum

of impoverished effects. Logia, abolition, anhedonia and decreased attention. The ability of typical antipsychotic to improve negative symptoms is controversial. Early studies found that negative symptoms were resistant to treatment (Coryell et al., 1990). Though some more resent studies suggest a modest beneficial effect depending on the dose in contrast, atypical antipsychotic may yield specific improvements in negative symptoms. In present work Clozapine were found to be superior over Haloperidol. The highly significant result was obtained with Clozapine (Davies et al., 1991; Mancama et al., 2002).

A more recent study determined that the optimum Haloperidol blood level to reduce regative symptoms was between 18 - 25 ng/mL. Levels outside of this range had nearly no effect on negative symptoms. In the present study also Haloperidol used in the same range as 5 - 18 ng/mL (Coryell et al., 1998) reported that when doses used beyond this range proved to have no effect on negative symptoms and thus justified.

Receptor systems involved in antipsychotic treatment

Our current understanding of the etiology of schizophrenia suggests the presence of a multifactorial genetic deficit, which can be triggered by perinatal environment factors. These processes result in neuronal defect. The best regarded hypotheses of abnormal neurotransmitter function include the dopaminergic, serotonergic (5-HT) (Canton et al., 1990; Jardemark et al., 2002), and glutamatergic system, apparently linked to the therapeutic antipsychotic effect of antipsychotic drugs. Several possible definitions of atypical antipsychotic have been proposed that, in the addition to producing fewer EPS, atypical antipsychotic have the following clinical characteristics: 1.) greater efficacy in the treatment of overall schizophrenic psychopathology among those non-respective to typical antipsychotic: 2.) great negative symptoms efficacy and : 3.) less perturbation of serum prolactin (Moore and Tye, 1992; Kinon and Gilmore, 2001).

CLOZAPINE

Synthesis in 1960, Clozapine (Clozaril), is a member of the dibenzodiazepine class of antipsychotic. The drug had a pharma-cologic profile unlike standard antipsychotic and is labeled as atypical antipsychotics.

Clozapine was the first atypical antipsychotic. It revolutionized the conceptualization of the pharmacology of schizophrenia (Andreason, 1999) because it produced a better psychiatric response than typical narcoleptics, did not produce extrapyramidal side effects in human or animals, and did not increase serum Prolactin levels. In schizophrenia it improved both positive and negative symptoms (for example anhedonia, mutism, withdrawals, lack of thought content), whereas typical narcoleptic produced few benefit on the negative symptoms at standard doses (Angst et al., 1989).

Clozapine has also been used to treat tremor in patients with Parkinson disease and can be extremely effective (Factor and Fiedman, 1997) in a double-blind trial, Clozapine was shown to have an anti tremor effect comparable to that of benztropine.

Clozapine (mean 274. 2 mg/day; n = 490) had a greater preventive effect on suicidality among patients with schizophrenia or schizoaffective disorder at high risk for suicide than olanzapine (mean 16.6 mg/day; n = 490) in randomized, rater-blinded, multi-centre study ($P < 0.05$; a 22 - 24% improvement) (Meltzer, 1999).

Clozapine is an atypical antipsychotic agent of low propensity to produce extrapyramidal symptoms and tradive dyskinesia compared with classical drugs such as chlorpromazine and haloperidol, and low propensity to induce akathesia and hyperpro-lactinemia review on clozapine in patient with schizophrenia have been published previously in CNS drugs (Wagstaff et al., 1995) and pharmaco-economic (Meltzer, 1990). The clinical efficacy of Clozapine in patients with schizophrenia unresponsive to intolerant of previous antipsychotic treatment is well established. Response rates (>20% reduction in Brief psychiartic Rating Scale [BPRD] score to >36) of 30 - 75%, with significant improvement in both positive and negative psychotic symptoms, quality of lie and social functioning, have been reported in well designed trail in this patient group.

Clozapine acts preferentially on mesolimbic rather than nesos-triatal dopaminergic neurons. The reason for showing better antipsychotic effect at low incidence of EPS may be due to effect of Clozapine on mesolimbic relating its efficacy to produce low EPS due to neostriatal effect. Dysfunction of the serotonergic system may be associated with suicidality (Roggenback et al., 2002). Clozapine modulates the relationship between serotonin, dopamine and norepinephrine and their metabolites in the brain (Hu et al., 1991). Present study is in accordance; there was not a single case of suicidal attempt or committing suicide, because clozapine improves serotonergic neurotransmission. Clozapine produces homeostasis of neurotransmission (Jansen, 1994). Increased weight gain has been associated with clozapine therapy (Henderson, 2001). Their effects of clozapine on the serotonergic system are responsible for appetite and food intake (Mancama et al., 2002) using data from the Framingham Heat Study. Increase weight gain is also directly related to increased effectiveness of antipsychotics (Lamberti et al., 1992). Present study reports weight gain of almost all patients on clozapine. Our results support theory that weight gain was correlated to effectiveness. Such a relationship was first suggested by, who reported a significant correlation between weight gain and improvement in the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The purpose of the present study was to test the hypothesis that clozapine in duce weight gain is related to its antipsychotic efficacy using multiple regression to control for initial severity of illness since clinical response in this population is often a function of initial level of psychopathology (Thomas, 1994). It is predicted that weight change and improvement in psychopathology would be directly related, that is that patients who gained the most weight would show the greatest improvement in psychopathology. Severity of illness and psychopathologic feature were assessed with the BPRS (Leadbetter et al., 1992), Schedule for affective disorder and schizophrenia – change (SADS-C), Global Assessment of function scale (GAFS), Scale of the assessment of negative symptoms (SANS), Scale for the Assessment of positive symptoms (SAPS) (Andreasen, et al., 1990) and Quality of Life Scale (QLS) (Heinrichs et al., 1994). Clinical trials demonstrate that the antipsychotic effect of clozapine was usually equal to or greater than that of the more conventional narcoleptics such as chlorpromazine and haloperidol. It is the first antipsychotic that demonstrated a significant effect on negative symptoms, as well as reducing anxiety and tension (Meltzer, 1992). Among all available narcoleptics, clazapine is considered to be least likely to induce TD. It is an atypical neuroleptic but also produce effect like anticholinergic actions, antiserotonergic actions and interaction with GABergic system. The drug may also be more D_1 selective than classical narcoleptics. Clozapine has been shown to bind with uniquely high affinity for the cloned and sequenced and mesolimbic specific D_4 schizophrenic brain (Vinivk and Kozlowski, 1986), being effective in around 60% of all patients with treatment-resistant disease (Meltzer, 1997). Clozapine is widely regarded as the gold standard treatment for treatment-resistance schizophrenia.

RESULTS

Over all treatment groups (Table 1 - 4) did not differ stat-

Table 1. Brief Psychiatric Rating Scale (BPRS) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	BPRS Scores (Mean ± SD)			P-Value	
		Baseline	2nd week	8th week	BL-2wks	BL-8wks
Haloperidol	8	42.6 ± 12.63	49.8 ± 11.50	47.2±11.50	0.249	0.544
Clozaril	8	63.4 ± 22.79	38.0 ± 20.94	38.0 ± 15.39	0.045	0.013

Table 2. Positive and Negative syndrome Scale (PANSS) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	PANSS Scores (Mean ± SD)			P-Value	
		Baseline	2nd week	8th week	BL-2wks	BL-8wks
Haloperidol	8	83.7 ± 24.39	94.0 ± 17.43	91.0 ± 19.57	0.176	0.483
Clozaril	8	95.3 ± 40.64	76.6 ± 32.52	54.6 ± 19.10	0.039	0.006

Table 3. Extra pyramidal rating scale (EPSRS) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	EPSRS Scores (Mean ± SD)			P-Value	
		Baseline	2nd week	8th week	BL-2wks	BL-8wks
Haloperidol	8	21.1 ± 6.45	19.8 ± 6.49	18.4 ± 6.16	0.420	0.204
Clozaril	8	22.3 ± 6.78	18.8 ± 7.40	13.8 ± 2.67	0.068	0.009

Table 4. Quality of life BREF (Who-QOL-BREF) according to treatment at baseline, 2nd week and 8th weeks.

Treatment Group	Subjects	Who-QOL-BREF Scores (Mean ± SD)			P-Value	
		Baseline	2nd week	8th week	BL-2 wks	BL-8 wks
Haloperidol	8	66.8 ± 6.45	75.2 ± 11.55	74.4 ± 14.18	0.068	0.134
Clozaril	8	67.8 ± 6.78	78.1 ± 11.68	89.4 ± 10.64	0.982	0.489

istically significantly with respect to any patient characteristic, illness characteristics, or base line severity of illness rating score. Patient were generally in their late 30 s (mean age 38). Majority of the patients were of the schizophrenia with psychosis.

Mean changes from baseline was used to compare illness severity changes for the four treatment groups. With regard to overall symptomatology (BPRS-total score and PANSS, EPSRS total score) Olanzopine was statistically significant showing maximum benefit and superior to the conventional agent. Mean changes in Olanzapine treated patients showed that they improved steadily through 2nd week of treatment, where as Haloperidol treated patients remained essentially unchanged. Statistically significant baseline to end point within treatment group improvement was observed for the Clozapine treatment group on all efficacy measures. The Table 1 - 4, which display the severity of primary rating for overall symptoms BPRS), clozapine showing maximum benefit. Mean changes in clozapine treated patients showed that they improved steadily through 2nd week to treatment, where as haloperidol treated patients remained essentially unchanged (Figure 1)At end point, the difference in changes from baseline was marginally significant. Positive and negative symptoms (PANSS), according to figure clozapine and olanzapine produce statistically significant results. Clozapine was found superior as it produced marked improvement in PANSS. Clozapine is administered orally; the initial recommended dose is 12.5 mg once or twice daily increasing (by 25 - 50

mg/day) to target doses of 300 - 450 mg/day. The improvement in mean score of PANSS was seen in clozapine group versus haloperidol at a mean of 36.5 mg/day. EPRS, clozapine and olanzapine both shows significant improvement in EPS. Clozapine has also been observed to reduce the abnormal dystonic movements and actually decreases the severity of TD and marked improvement in tremors. And QOL scale, Quality of life is psychological and social functioning. Increase in the total count means an improvement in the symptoms and hence in the quality of life reflects visit wise observed case analysis mean changes from baseline to endpoint in QOL scores for the acute or maintenance phases are shown in Table 4. Clozapine treated patients had significantly greater mean improvement compared to Haloperidol-treated patients in the common Objects and Activities subscale (p = 0.039) of QOL scale during the acute phase. In the maintenance phase, Clozapine-treated patients hand greater functional improvements corresponding to significant mean increase in the QOL total score. The colzapine treatment group demonstrated numeric decrease from baseline on all four scales. Therefore week 8 results reflect an analysis of completers. It is evident from the table that clozapine is found to be superior in showing improvement in the negative as well as positive symptoms with significant P values where as there is no significant change or deterioration in symptoms with Haloperidol. Clozapine has also been observed to reduce the abnormal dystonic movements and actually decreases the severity of Trainee Dyskinesia (TD) and an improvement in tremors. These mean changes, represented graphically, are dis-tinct from those described under End-point analysis since and end point analysis is based on last-observation-carried-forward data (using every patient's last score).

Conclusion

Presently study suggests that atypical antipsychotic like clozapine has lower incidence of EPS than the conventional agent Haloperidol. In addition to schizophrenia, clozapine is also suitable for patients of P.D (Parkinson's disease). Clozapine did not cause any significant blood dyscrasias. Present study suggests that atypical antipsychotics have lower incidence of EPS than narcoleptics, we can speculate that Haloperidol has far more adverse effects and higher incidence of EPS and TD than clozapine. The ability of clozapine to produce lower EPS is based on receptor affinity. Clozapine induced weight gain is directly correlated to its clinical response. Acute dystonia, akathesia and parkinsonism (assessed with the standard rating scales) were significantly less frequent with Clozapine (mean dosage 12 mg/day) than with moderately high doses of haloperidol. Also reduces the severity of already presented TD, and showed antipsychotic benefits in patients with psychosis and parkinsonism disease (PD) as compared to Haloperidol.

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