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Effect of Antipsychotic Treatment on Clinical Profile in Patients with Schizophrenia

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ABSTRACT
Schizophrenia is a debilitating condition that affects 1% of the population world wide. There is dopaminergic pathophysiology as per the dopamine (DA) hypothesis. We studied the efficacy of antipsychotic treatment in patients with schizophrenia as measured by Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Severity (CGI-S) Scales, Calgary Depression Scale for Schizophrenia (CDSS) in a prospective hospital based study in which 141 cases of schizophrenia were enrolled who were receiving antipsychotic medications as per decision of the treating psychiatric units. Baseline data and data at two-four and six weeks was collected for all subjects using PANSS, CGI-S and CDSS. The results showed that the patients with schizophrenia showed significant improvement in PANSS scores (positive, negative, general psychopathology and total scores) and in CGI-S scores after six weeks of treatment with antipsychotics. Thus, antipsychotics improve symptoms in schizophrenia patients by acting on the dopamine pathway thereby providing evidence to the dopamine hypothesis of schizophrenia. Schizophrenia, antipsychotic medications dopamine hypothesis PANSS, CDSS.

INTRODUCTION

Schizophrenia is a chronic mental illness condition affecting 1% of the population worldwide. Symptoms of schizophrenia are divided into positive and negative symptoms. Positive symptoms include hallucinations, paranoia and delusions while negative symptoms include reduced motivation, impoverished speech, blunt affect and social withdrawal. These symptoms usually appear in early adulthood and often persist in around three-quarters to two-thirds of patients despite adequate treatment[1]. The chronic course of illness not only leads to individual distress but also acts as a high societal burden. Apart from the morbidity, it also leads to a two-three fold higher mortality rate as compared to the general population[2].

Therefore there is a need to continually develop and evaluate novel treatments for this disorder not only for the benefit of the patients but also for the wider society. As of now antipsychotics are the mainstay of treatment for patients with schizophrenia. The antipsychotics, by acting on the dopamine pathways lead to the dopamine hypothesis of schizophrenia. This enduring theory of schizophrenia has evolved over time and was first based upon clinical observations and subsequently empirical evidence from anti-psychotic treatment studies[3].

Mechanism of antipsychotic action: All antipsychotics act by D2 receptor antagonism this has given rise to the hypothesis that schizophrenia involves a dysregulation of dopaminergic circuits with excess dopaminergic activity in the mesolimbic pathway (leading to positive symptoms of psychosis) and reduced dopaminergic signalling in the mesocortical pathway (leading to negative symptoms).

The dopamine hypothesis is not only supported by the efficacy of dopamine receptor antagonists but also by the effects of dopamine agonists like amphetamine which precipitate psychosis and the effects of dopamine-depleting agents like reserpine in improving psychotic symptoms[4].

Antipsychotic action has consistently been shown to occur when the occupation of striatal D2 receptors is more than 65% but further increases in the level of D2 blockade are not associated with improved antipsychotic efficacy rather it leads to the onset of side effects such as Extra-Pyramidal Side Effects (EPSEs) and hyperprolactinaemia. A threshold dose for EPSEs occurs when 80% of the D2 receptors are occupied and for hyperprolactinaemia when D2 blockade exceeds 72%[5]. Inspite of the association between striatal dopamine blockade and the risk of EPSEs, it becomes important to know that it is the mesolimbic brain system which is the critical site of action for therapeutic effect and not the striatal dopamine blockade. Our aim was to study the efficacy of antipsychotic treatment in patients with schizophrenia as measured by PANSS and CGI-S.

MATERIALS AND METHODS

The study was conducted at the Central Institute of Psychiatry, Ranchi. It was a prospective hospital based study. Sample consisted of 150 cases of schizophrenia according to Diagnostic Criteria for Research (DCR) of International Classification of Diseases-tenth edition (ICD-10 World Health Organization, 1993) using purposive sampling technique. All the patients received antipsychotic medications as per the decision of the treating psychiatric units. Inpatients satisfying criteria of Schizophrenia according to Diagnostic Criteria for Research(DCR) of International Classification of Diseases-tenth edition (ICD-10 World Health Organization. 1993) between age 18-60 years of either sex who were willing to give written informed consent were included in the study. Patients with co-morbid neurological or psychiatric disorder(s), history of substance abuse (except nicotine and caffeine), history of epilepsy, significant head injury or any neurosurgical procedure were excluded from the study.

Tools and materials for the study: Socio-demographic and clinical data sheet. It includes various socio-demographic variables like name, age, sex, religion, educational qualification, occupation, income, marital status, family type, residence and clinical variables like age of onset, duration of illness, treatment history, past history and family history and the clinical data relevant to the present study.

Positive and negative syndrome scale[6]: The PANSS includes 30 items on three subscales. Seven items for positive symptoms, seven for negative symptoms and 16 covering general psychopathology. The items are rated on a seven point continuum (1: Absent, 7: Extreme). This scale is a standard tool for assessing clinical outcome in schizophrenia studies.

Clinical global impressions-severity (CGI-S) scale[7]: The severity of illness is rated on a 7-point scale. It is applicable for all research populations. For severity of illness, one pretreatment and one post treatment assessment is required.

Calgary depression scale for schizophrenia[8]: It is an observer scale which assesses depressive symptoms in schizophrenia. It contains 9 items and score is obtained by adding each of item scores.

Procedure: Written informed consent from the patients was taken after explaining the objectives and procedure of the study in detail. A detailed physical

examination was done to rule out any major medical or neurological illness. Relevant socio-demographic and clinical data were collected from all the participants on the socio-demographic and clinical data sheet. Patients received antipsychotics as per naturalistic study design based on the decision of the treating team. Baseline data and data at two-four and six weeks was collected for all the subjects using Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Severity Scale (CGI-S) and Calgary Depression Scale for Schizophrenia (CDSS). Nine patients from the control group were dropped from the study as six were discharged on request by the guardian prior to completion of the study, diagnosis was revised in two patients and one patient developed medical complication. Ultimately 141 subjects were analyzed.

Statistics: Statistical analysis was done using IBM SPSS version 22.0. The entire socio-demographic and clinical characteristics for continuous variables were compared using the student t-test. For categorical variables, chi-square fisher's exact test were used. Repeated measures ANOVA was used to study the effect of time on the PANSS, CGI-S and CDSS scores in the sample.

RESULTS

Table 1 shows the effect of time baseline, 2-4-6 weeks on PANSS scores in the subjects. Using repeated measures ANOVA, it was seen that the effect of time was significant on the PANSS positive scores ($p<0.001$) PANSS negative scores ($p<0.001$) PANSS general psychopathology scores ($p<0.001$) and PANSS total score ($p<0.001$). There was a significant decrease in PANSS positive, PANSS negative, PANSS general psychopathology and PANSS total score from baseline to final (i.e., after 6 weeks) in the subjects ($p<0.001$).

Table 2 shows the effect of time (baseline, 2weeks, 4weeks and 6 weeks) on CGI-S scores in the subjects**.** There was a significant difference in CGI- Severity scores over time ($p<0.001$). There was a significant decrease in CGI-S scores from baseline to final (i.e. after 6 weeks) in the subjects ($p<0.001$). Table 3 shows the effect of time (baseline, 2 weeks, 4 weeks and 6 weeks) on CDSS scores in the subjects. There was a significant difference in CDSS scores over time ($p<0.001$). There was a significant decrease in CDSS score from baseline to six weeks following antipsychotic treatment in the subjects ($p<0.001$).

DISCUSSIONS

Role of antipsychotics in the treatment of schizophrenia There was a significant decrease in PANSS positive, negative, general psychopathology and total scores from baseline to six week in the subjects (Table 1). This is in line with various previous studies which have observed that there is a reduction in PANSS scores (positive, negative, general psychopathology and total) with antipsychotics[9-10]. Similarly with time, there was a reduction in clinical severity as measured by CGI-S scores (Table 2). These findings are in agreement with various studies which reported a reduction in CGI scores in patients with schizophrenia receiving antipsychotics[11-12].

Thus the results of this study support the dopamine hypothesis of schizophrenia which postulates that dysregulation of dopamine gives rise to positive, negative and cognitive symptoms of schizophrenia. Hyperactivity of dopamine neurotransmission in the mesolimbic pathway contributes to positive symptoms while hypofunctionality of dopamine neurotransmission in the prefrontal cortex contributes to the negative and cognitive symptoms of schizophrenia. Treatment with antipsychotics improves these symptoms by acting on these dopamine pathways.

Table 1: Mean effect of time (i.e. baseline, 2 weeks, 4 weeks, 6 weeks) on PANSS scores

	Baseline Mean±SD	2 Weeks Mean±SD	4 Weeks Mean±SD	6 Weeks Mean±SD	Effect/Time			
Variables	(N = 141)	(N = 141)	(N = 141)	(N = 141)	F	P	$pEta^2$	P
PANSS Positive	27.30±5.77	25.10±5.39	21.60±5.24	19.40±5.32	76.102	0.000*	0.800	1.000
PANSS Negative	28.95±7.13	27.05±6.94	25.25±6.97	23.75±6.60	62.768	0.000*	0.768	1.000
PANSS General psychopathology	50.25±11.21	46.00±8.98	41.95±8.40	39.25±8.56	43.334	0.000*	0.695	1.000
PANSS Total	106.35±18.50	98.25±16.07	85.75±24.05	82.60±15.86	33.182	0.000*	0.636	1.000

*p<0.001, P: Observed power, $pEta^2$: Partial Eta square

Table 2: Mean effect of time (i.e. baseline, 2 weeks, 4 weeks, 6 weeks) on CGI-S scores

	Baseline Mean±SD	2 Weeks Mean±SD	4 Weeks Mean±SD	6 Weeks Mean±SD	Effect/Time			
CGI-S	(N = 141)	(N = 141)	(N = 141)	(N = 141)	F	P	$pEta^2$	P
PANSS positive	5.70±.47	5.00±.46	4.35±.59	3.65±.75	100.429	0.000*	0.841	1.000

*p<0.001, P: Observed power, $pEta^2$: Partial Eta square

Table 3: Mean effect of time (i.e. baseline, 2 weeks, 4 weeks, 6 weeks) on CDSS scores

	Baseline Mean±SD	2 Weeks Mean±SD	4 Weeks Mean±SD	6 Weeks Mean±SD	Effect/Time			
CDSS	(N = 141)	(N = 141)	(N = 141)	(N = 141)	F	P	$pEta^2$	P
PANSS positive	2.40±1.82	1.55±1.36	1.15±1.35	0.85±1.23	19.375	0.000*	0.505	0.999

*p<0.001, P: Observed power, $pEta^2$: Partial Eta square

Effect of antipsychotics on depressive symptoms: With time, significant improvement was seen on CDSS scale in the patients (Table 3) which is consistent with the findings of several studies which studied the effects of the different antipsychotics on depression in schizophrenic patients and found significant improvements on Calgary Depression Scale for Schizophrenia[13-14]. There are various reasons why atypical antipsychotics may seem to improve depressive symptoms in patients with schizophrenia. First, since akinesia and akathisia are frequently confused with depression in schizophrenia, hence the propensity of atypical antipsychotics to cause a lesser extent of extrapyramidal side effects leads to improvement in affective symptoms[15]. Second, since atypical antipsychotics do not depend exclusively on dopamine blockade for their therapeutic effects[16] they might evade the neuroleptic-induced dysphoria which contributes to the depression symptoms seen in patients with schizophrenia. Third, atypical antipsychotics have been observed to be better than the typical antipsychotics in the treatment of negative symptoms[17] which sometimes appear like depression.

Thus, antipsychotics bring about improvement in the positive and negative symptoms of schizophrenia by acting on the dopaminergic pathways. In addition, they improve depressive symptoms in the patients with schizophrenia.

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