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Research Article

A STUDY TO EVALUATE THE SAFETY OF ARIPIPRAZOLE IN TREATMENT OF SCHIZOPHRENIA

ABDUL FAHEEM KHAN[1], OMPRAKASH RAICHANDANI[2], SAPNA RAICHANDANI[3], KHANETA PARVEEN[4]*

[1]Department of Pharmacology, Chirayu Medical College and Hospital, Bhopal, Madhya Pradesh, India. [2]Department of Psychiatry, NSCB Medical College Jabalpur, Madhya Pradesh, India. [3]Pharm. Honorary Lecturer, Shri Ram College of Pharmacy, Jabalpur, Madhya Pradesh, India. [4]Department of Pathology, Chirayu Medical College and Hospital, Bhopal, Madhya Pradesh, India. E-mail: drkhaneta@gmail.com

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ABSTRACT

Objectives: Aripiprazole is recommended in a dose of 10 and 15 mg/day, with a dose ranging between 10 and 30 mg/day in the treatment of schizophrenia. The primary objective of the study is to evaluate the safety profile of Aripiprazole in low dose of 15 mg versus high dose of 30 mg in the treatment of Schizophrenia.

Methods: A total of 60 patients (not on treatment) between age 18-60 years of either gender who meet the diagnostic criteria as per DSM-IV classification for schizophrenia and schizoaffective disorder. All patients were randomly divided into two groups on single-blind study criteria. Group-I: Aripiprazole 15 mg once a day, morning dose for 6 weeks. Group-II: Aripiprazole 30 mg once a day, morning dose for 6 weeks. The ESRS includes 12 questionnaire items; each item is rated on a 7-point scale. Efficacy assessment included at baseline and at 6 weeks end study scoring on PANSS, EPRS, and CGI.

Results: The total number of patients showed the ESRS (total symptoms) in group-I was 09 patients (35%) out of 26 and in group II, 13 patients (59%) out of total 22 showed the ESRS (total symptoms). In both the groups aripiprazole showed the comparable efficacy by improving overall symptoms in the number of patients. In group I, 20 patients have shown the improvement in overall scores of all scales. In group II, 16 patients have shown the improvement in overall scores in different scales.

Conclusions: Aripiprazole is effective in schizophrenia and schizoaffective disorders, doses of 15 mg are equally effective as doses of 30 mg, side effects like EPS are more with higher doses of Aripiprazole.

Keywords: Aripiprazole, Dose, Schizophrenia.

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INTRODUCTION

Schizophrenia and schizoaffective disorders are quite common in young adult population, with higher incidence rate of chronicity, morbidity, and suicidal tendency. Both typical and atypical antipsychotic drugs are used for the treatment of schizophrenia [1,2].

Aripiprazole is a prototype of the 'third generation' antipsychotics – the so-called dopamine– serotonin-system stabilizers (DSS). It is claimed to be at least as effective as haloperidol in the treatment of positive and negative symptoms of schizophrenia, and it may cause fewer adverse effects. Aripiprazole is reported to be useful in all phases of schizophrenia, and to enhance cognitive functions [3].

Aripiprazole 10–30 mg/day is generally well tolerated [4]. The tolerability profile of aripiprazole is broadly comparable to that observed with placebo in a meta-analysis of short-term trials in patients with acute relapse of schizophrenia or schizoaffective disorder and in a 26-week trial in patients with chronic stable schizophrenia [5].

Objectives

The primary objective of the study is to evaluate the safety profile of Aripiprazole in a dose of 15 mg versus a dose of 30 mg in the treatment of Schizophrenia.

METHODS

This study was conducted in department of Pharmacology and department of Psychiatry OPD at NSCB Medical College Jabalpur (Madhya Pradesh) India, enrolled patients of either gender aged 18–60 years.

In the previous studies by various researchers on Aripiprazole in schizophrenia, it has shown good efficacy with low side effects profile in therapeutic doses when compared with other antipsychotic drugs. Thus, an attempt has been made to study the response of Aripiprazole in various types of schizophrenia and to study the safety of Aripiprazole, and to compare the safety of Aripiprazole in low doses of 15 mg versus high dose of 30 mg. This study comprised of all the new and old patients of age group between 18–60 years of either gender who meet the diagnostic criteria as per DSM-IV classification for schizophrenia and schizoaffective disorder [6].

Selection criteria

- Inclusion criteria: (i) all the new and old patients (who are not on any treatment) of either sex who met the diagnostic criteria as per DSM-IV classification for Schizophrenia or Schizoaffective disorder were taken in the study. (ii) Those patients and their relatives who are willing to give consent for the treatment.
- Exclusion criteria: (i) Schizophrenic patients who are taking any antipsychotic drug treatment in the last one month. (ii) If the subject is women who is pregnant or breast feeding or at risk of pregnancy during therapy. (iii) If the patient consume alcohol or have drug dependency in the last 6 months. (iv) If the patient is on ketoconazole carbamazepine, levodopa, dopamine agonist, diuretic therapy or is at risk of torsade-de-pointes. (v) Patient hypersensitive to antipsychotic drugs like aripiprazole. (vi) If the patient is suffering from hepatic,

renal, metabolic, or neurological disorders (Parkinson's disease or other movement disorders). (vii) ECG with long QT interval.

Study design

All the new and old patients of Schizophrenia and Schizoaffective disorder who met DSM-IV criteria and not treated by any antipsychotic drugs in past one month is to be taken on all OPD days. Prior written informed consent from each patient and their relative's enrolled in this study was taken. The patients who were already on treatment were excluded from the study.

Study schedule and plan

A total of 60 patients were taken in the study. Each patient has undergone detailed Psychiatric and medical history with clinical examination. Efficacy assessment included at baseline and at 6 weeks end study scoring on positive and negative symptoms scale (PANSS), extrapyramidal rating scale (EPRS) and clinical global impression (CGI) was done. The PANSS is 30 items rating scale that is specifically developed to assess individuals with Schizophrenia. The CGI is one of the most widely used brief assessment tools in Psychiatry. This is a 3-item scale which measures overall illness severity. Repeated, it can evaluate response to treatment. The ESRS includes 12 questionnaire items to identify subjective symptomatology; each item is rated on a 7-point scale.

These patients were randomly divided into 2 groups on single blind study criteria

- Group-I: Patients prescribed tablet Aripiprazole 15 mg once a day, morning dose for 6 weeks.
- Group-II: Patients prescribed tablet Aripiprazole 30 mg once a day, morning dose for 6 weeks.

Clinical efficacy

Efficacy and safety data of aripiprazole was compared every week for 6 weeks by applying the 3 standard scales on the patients, these scales were PANNS, EPRS and CGI. Improvement was considered when reduction of >50% score on PANSS on 6th week from baseline. When rating on CGI scale is in between 2-3 at 6 weeks of treatment, it shows the improvement. Safeties of the two doses of Aripiprazole in two groups were studied on ESRS scale such as Parkinsonism, Akathisia, Dystonia and Dyskinesia.

Assessment of efficacy and safety

The analysis of efficacy and side effects of 15 mg versus 30 mg of Aripiprazole was compared on demographic, efficacy, and safety profile by using appropriate statistical tests of significance. All reported adverse drug reactions in the study population were analyzed for their severity, duration, and relation to the study drug.

Statistical analysis

The results were statistically analyzed by students t test, paired t test, and Chi-square test.

RESULTS

In this study mean age group of patients was 27–32 years, it means the young age group is most affected. There was no statistically significant difference between the two groups for age, gender, marital status, rural and urban factors. (Table 1) A total number of patients were 60, number of dropout patients were 12, 8 patients did not complete the study due to lack of follow-up. Four patients were dropped out due to adverse effects, i.e., extrapyramidal symptoms (EPS).

Safety

In this study the total number of patients showed the ESRS (total symptoms) in group-I is 09 patients (35%) out of 26, and in group-II 13 patients (59%) out of total 22 showed the ESRS (total symptoms). In group-I total number of symptoms of ESRS including Parkinsonism, Akathisia, dystonia, and dyskinesia were included and it shows 35% of patients affected by adverse effects. In group-II 59% of patients show the same symptoms of EPRS.

In group-I patients with Parkinsonism were 10, Akathisia 12, dyskinesia 07, and dystonia 0 patients out of total 26 patients. In group-II, 15 patients of Parkinsonism, 16 patients of Akathisia, 09 patients of dyskinesia, and 02 patients with dystonia were analyzed (Table 2).

In group-II maximum number of patients showed the EPRS total symptoms in which parkinsonism and Akathisia is maximum with low incidence of dystonia. In group-I also the maximum number of patients showed the parkinsonism and Akathisia but no incidence of dystonia. The overall ESRS is more in group-II with 30 mg in comparison with group-I with 15 mg dose. Although, there is no statistically significant difference in two groups for the total number of patients showing Parkinsonism were more in group-II with increased severity. In group-I, 10 patients out of 26 shows Parkinsonism and in group-II, 15 patients out of 22 showed Parkinsonism. The symptoms of Parkinsonism are higher in group-II in comparison with group-I. The higher dose of 30 mg in group-II showed the increase incidence and severity of Parkinsonism.

In group-I, 12 patients out of 26 presents with Akathisia and in group-II, 16 patients out of 22 presents with Akathisia were observed. There is statistically significant difference between the two. In this study, there is a high incidence of Akathisia in group-II compared with group-I.

In group-I, 07 patients present with dyskinesia out of 26 and in group-II, 09 patients present with dyskinesia out of 22 patients. In this study, there is high incidence rate with increase severity of dyskinesia is analyzed in group-II with 30 mg dose and low incidence of dyskinesia with group-I. In this study, 02 patients have dystonia, which is on 30 mg dose and with 15 mg dose no patient has dystonia. There is no incidence of dystonia with low dosage of 15 mg in group-I in comparison to group-II with 30 mg of Aripiprazole. In group-I with 15 mg dose of Aripiprazole the peak of the severity of EPRS was present in the second and third week of therapy and thereafter it decreased. In group-II with 30 mg dose, the peak of severity was present in the first and second

Table 1: Demographic profile

Parameters	Group-I (dose 15 mg) n=30	Group-II (dose 30 mg) n=30
Age (mean)	32 years	27 years
Gender		
Males	22	19
Females	08	11
Marital status		
Married	12	10
Unmarried	18	20
Geography		
Rural	15	20
Urban	15	10
Dropout patients	04 patients	08 patients

Table 2: Extrapyramidal symptoms

Groups	Parkinsonism (p<0.05)		Total no. of patients treated
	Present	Absent	
Group-I (15 mg)	10	16	26
Group-II (30 mg)	15	07	22
Akathesia (p=0.02)			
Group-I (15 mg)	12	14	26
Group-II (30 mg)	16	06	22
Dyskinesia (p<0.05)			
Group-I (15 mg)	07	19	26
Group-II (30 mg)	09	13	22
Dystonia (p=0.001)			
Group-I (15 mg)	0	26	26
Group-II (30 mg)	02	20	22

week of therapy. Akathesia was more common and severe with 30 mg of Aripiprazole (p=0.02). Other types of EPS more common with 30 mg but not reached the level of significance. Peak presentation of EPRS in the first week with 30 mg, however in 2nd or 3rd week with 15 mg dose of Aripiprazole (Table 3).

The overall ESRS is more in group-II with 30 mg in comparison with group-I with 15 mg dose. Although, there is no statistically significant difference in two groups for the total number of patients showing Parkinsonism were more in group-II with increased severity. In group-I, 10 patients out of 26 shows Parkinsonism and in group-II, 15 patients out of 22 showed Parkinsonism. The symptoms of Parkinsonism are higher in group-II in comparison with group-I. The higher dose of 30 mg in group-II showed the increase incidence and severity of Parkinsonism. In group-I, 12 patients out of 26 presents with Akathisia and in group-II, 16 patients out of 22 presents with Akathisia were observed. There is statistically significant difference between the two. In this study, there is high incidence of Akathisia in group-II compared with group-I.

Grades of severity of EPRS

In group-I the total number of patients present with EPRS such as Parkinsonism, akathesia, dystonia, and dyskinesia were of mild grade of severity but in group-II the total number of patients present with EPRS are of moderate to severe grade of severity. In group-I no incidence of dystonia but in group-II, 2 patients with moderate grade of severity were present.

Efficacy

Efficacy results has been published previously as 'EFFICACY OF ARIPIPRAZOLE IN TREATMENT OF SCHIZOPHRENIA IN POPULATION OF CENTRAL INDIA' in year 2020 by an author Dr. Omprakash Raichandani *et al*. International Journal of Medical and Biomedical Studies. Volume 4, Issue 1; January: 2020; Page No. 265-268. This current publication is the extension of the same study publication with a primary objective to highlight the safety profile of Aripiprazole in schizophrenia. For the efficacy results please refer to the above-mentioned study as a primary reference source [6].

DISCUSSION

The maximum numbers of cases of Schizophrenia were found in young age group. However, in another study by Kane *et al*. 2002, there is an equal incidence of Schizophrenia among male and female patients. In a study by Kane *et al*., dropout rate for 15 mg dose was 33% and 45% with 30 mg dose. However, in our study dropout rate in group-I with 15 mg dose was 7% and 13% in group-II with 30 mg dose. In a study by Kane *et al*., the reduction of total PANSS score >30% from baseline to the end study shows the improvement and efficacy of the drug [5]. However, in this study Aripiprazole is equally efficacious between the two groups with different doses in various types of schizophrenia and schizoaffective disorder [7].

Table 3: Peak of presentation of EPRS (Weeks) maximum severity with 15 mg dose

Peak of EPRS with 15 mg dose						
Type of ESR	**1st wk**	**2nd wk**	**3rd wk**	**4th wk**	**5th wk**	**6th wk**
Total ESRS		++	+++			
Parkinsonism	+++	+++	++++			
Akathesia		+++	++++			
Dystonia	-	-	-	-	-	-
Dyskinesia		++				
Peak of EPRS with 30 mg of dose						
Total ESRS	+++					
Parkinsonism	++++	+++	++			
Akathesia	++++	+++				
Dystonia	++	++	++			
Dyskinesia	+++		++			

In our study, the episodes of schizophrenia do not show any major statistically significant difference in between two groups of low doses (15 mg Vs 30 mg) and high dose of Aripiprazole. Although, the patients with 1st episode of schizophrenia in comparison to multiple episodes showed a good efficacy with both the doses of aripiprazole.

In a study by Kane *et al*. 2003; >50% of patients with schizophrenia were improved with Aripiprazole in both the groups [7]. However, in our study there was >50% reduction in PANSS positive score from baseline to 6 weeks of study.

A study by Kane *et al*. shows a responder analysis with response rate of >30% reduction in PANSS total score from baseline to end study found significantly greater response rate for patients in both groups [7]. In our study >60% of patients were improved and shows efficacy with both the doses of Aripiprazole in both the groups. There is >30% reduction of score from baseline to the 6th week study. In a 4-week trial by Kane *et al*., 2003, a response rate was defined as a >30% decrease from baseline score to the end study in the PANSS total score [5]. However, in our study there is >50% reduction in PANSS total which shows efficacy of aripiprazole in both the groups.

Limitations of the study

However, less sample size, single blinded study, lacking placebo as a control group are few drawbacks and limitations in this study, but the findings are worth considering in choosing the appropriate antipsychotic medications in the treatment of schizophrenia and schizoaffective disorder.

CONCLUSIONS

EPS is more with 30 mg dose in comparison to 15 mg dose of aripiprazole. Although, on ESRS scale (Parkinsonism, akathesia, dystonia, and dyskinesia) there is no statistically significant difference between the two groups except for Akathisia, which is high in group-II, the severity of side effects in group-II is more than the group-I.

Thus, we conclude that the Aripiprazole is effective in schizophrenia and schizoaffective disorder, low doses of 15 mg is equally effective as high dose of 30 mg, side effects like EPS are more with high doses, therapeutic efficacy is almost comparable with the two doses, but side effects are more with 30 mg dose.

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AUTHORS CONTRIBUTION

All authors have contributed to study design, manuscript writing and review, data analysis and article finalization.

CONFLICT OF INTEREST

None.

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