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EFFECT OF ARPIPRAZOLE ON AMISULPRIDE INDUCED HYPERPROLACTINEMIA IN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

Aripiprazole is a dopamine D2 receptor partial agonist with partial agonist activity at serotonin 5HT1A receptors and antagonist activity at 5HT2A receptors. The objective of this study was to evaluate the effect of Aripiprazole on hyperprolactinemia in adult schizophrenia patients induced by Amisulpride. The study sample consists of 53 patients, 18 to 50 years old treated for schizophrenia. Out of 53 patients, 35 patients had a normal prolactin level within 2 weeks, 9 patients within 4 weeks and 4 patients within 6 weeks and 2 patients within 8 weeks. However the prolactin level was not back to normal for 3 patients and one patient's prolactin level decreased below normal level. Amisulpridedose was not changed during the study period. Enrolled patients showed normal level of prolactin after augmenting the Aripiprazole in the treatment and the authors concluded that the addition of Aripiprazole rapidly normalizes the Amisulpride induced Hyperprolactinemia. The normalization of patient's prolactin level is highly statistically significance and the P value is less than 0.0001by conventional criteria (Student t-Test).

KEY WORDS: Prolactin,Hyperprolactinemia, schizophrenia. Amisulpride, Aripiprazole.

INTRODUCTION

The anterior pituitary secretes the prolactin that is under tonic dopaminergic control in the tuberoinfundibular tract[1].Dopamine suppresses the endocrine processes of prolactin via the dopamine 2 (D2) receptors on lactotrophs in the pituitary[2]. Antipsychotic drugs are known

to increase serum prolactin levels by blocking the D2 receptor in the tuberoinfundibular pathway. Antipsychotic drugs have various binding affinities toward the D2 receptor. Hyperprolactinemia is a disorder marked by the overproduction of prolactin in both men and non-pregnant women. Atypical antipsychotics such as Risperidone and Amisulpride[3,4] causes hyperprolactinemia which is manifested as lactation , menstrual problems (having no periods or irregular periods), vaginal dryness, hypogonadism, infertility and erectile dysfunction[5-7]The conventional antipsychotics are also associated with increase in the prolactin levels[8, 9] The recently introduced practical guidelines for the treatment of schizophrenia recommended several strategies for the resolution of antipsychotic-induced hyperprolactinemia and associated adverse effects[10,11]. Aripiprazole is a novelantipsychotic drug which exhibits potent partial agonist activity at the D2 receptors[12, 13]. It is thought to stabilize the dopaminergic system and ameliorate the symptoms of schizophrenia without elevating the serum prolactin levels[14].

MATERIALS AND METHODS

A prospective study was done on 53 patients with hyperprolactinemia taking Amisulpride were enrolled. There were 67 patients approached for this study, 6 patients were screen failure due to the normal levelof prolactin and 8 patients did not give consent in this study. The study was done at M.S.Chellamuthu Trust and Research Foundation and Radianz Health and Research Pvt Ltd and Ahana Hospitals, Madurai.The study was conducted for a period of 10 months and including 6 months of enrolment period. Inclusion criteria included Men, Non pregnant, Nonlactating women and aged 18-50 years with a primary diagnosis of schizophrenia (DSM-IV). Out of 53patients, 37 were male and 16 were female and Aripiprazole 10mg was added to the patient receiving 200-400mg/day of Amisulpride. The Amisulpride dose was not changed and in addition, Aripiprazole was dosed at 10 mg throughout the study period. The Aripiprazole treatment started after obtaining appropriate consent. The subsequent clinical response and follow up laboratory reports were recorded. Exclusion criteria included many antipsychotic in the patient current regimen other than Amisulpride.

Ethical Committee Approval

Ethical committee approval was sought from Institutional Ethics committee, Radianz Health care and Research, Madurai and Tamilnadu.

Statistics

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Graph Pad Instat DTCG Using these software frequencies, percentages, means, standard deviations, student t- test and 'p' values were calculated. The 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS AND DISCUSSION

Out of 53 patients enrolled in the study, 37 (70%) were male and 16 (30%) were female. (Table1)

Table 1 : Sex Wise Distribution

Gender	Total No.Of Patients
MALE	37
FEMALE	16

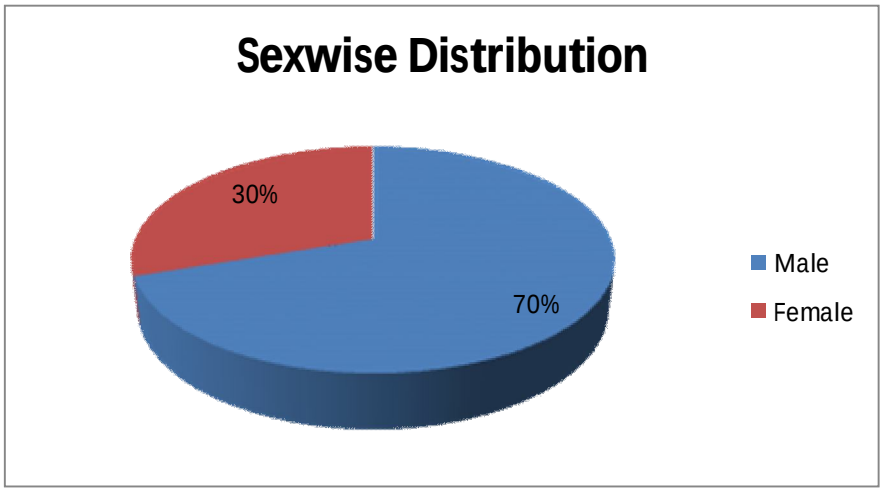

Figure –I: Pie chart showing sex wise distribution of the study

Patients enrolled for the study 6% of the patients were from the age group of (18-20), 28% (21-30), 36% from (31-40) and 30% from (41-50). (Table 2)

Table 2 : Age Wise Distribution

Age	Total No.Of Patients
18-20	3
21-30	15
31-40	19
41-50	16

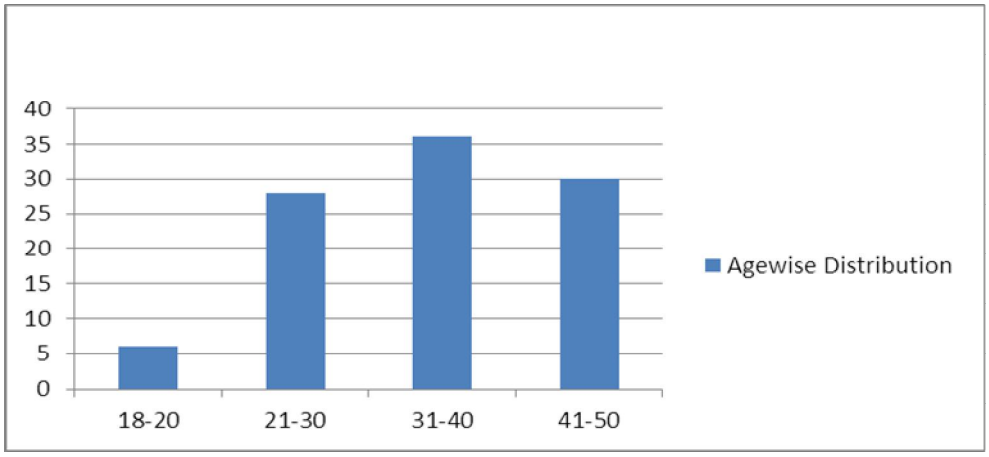

Figure –II: Bar diagram showing age wise distribution

Prolactin levels normalised within 2 weeks for 35 patients, 9 patients required within 4 weeks, 4 patients required within 6 weeks and 2 patients required within 6 weeks. The serum prolactin was obtained in the morning as fasting concentration. The sample was collected at the time of screening, week 2, week 4, week 6 and week 8. (Table 3)

Table 3 : Time Taken For Normalisation Of Prolactin

Weeks	Total No.Of Patients
2	35
4	9
6	4
8	2

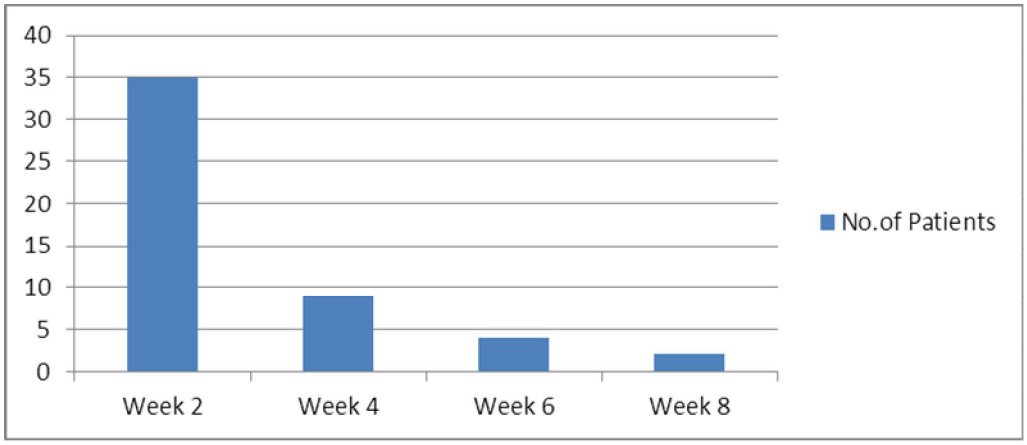

Figure –III :Bar diagram showing time taken for normalisation

The patients enrolled in the study since they had high levels of prolactin. They were receiving only Amisulpride and asymptomatic. Hence the drug has not been changed, then the Aripiprazole was added along with Amisulpride and the result is significant (Table 4).

Table 4 Normalisation Of Hyperprolactinemia

NORMALISATION OF HYPERPROLACTINEMIA	NO.OF PATIENTS
YES	50
NO	3

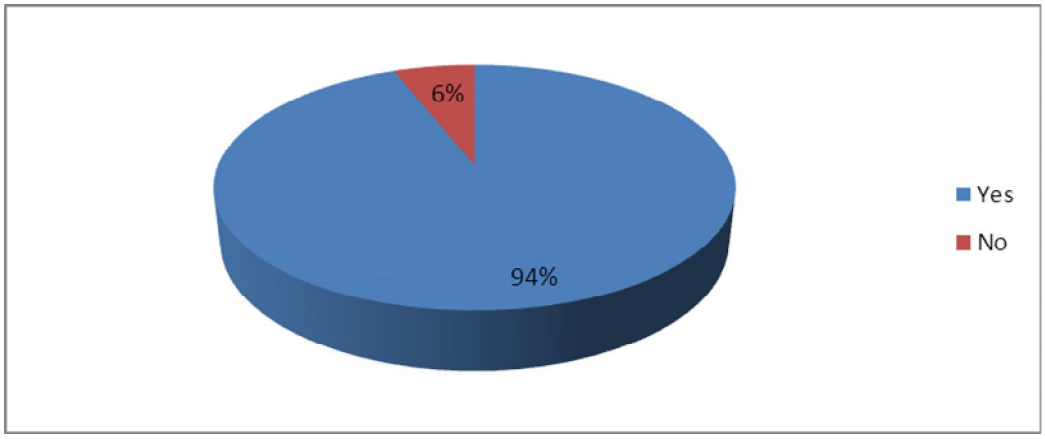

Figure –IV : Pie chart showing normalisation of hyperprolactinemia

Aripiprazole clearly had an effect on hyperprolactinemia while other antipsychotics induced it. Augmenting the Aripiprazole with Amisulpride, the mean prolactin levels decreased significantly (p<0.0001) at week 2 and were maintained till week-8 .Serum prolactin levels were significantly lower with Aripiprazole ($p < 0.0001$). The mean prolactin levels of men at the time screening was 32.8 ± 5.9 and at week 8, it has decreased to 10.7± 4.7.The mean prolactin levels of women at the time screening was 48.3± 5.9 and at week 8 it was further reduced to 20.8 ± 8.6.(Table5 and Figure 5).

TABLE 5 Mean Change from screening to Week 8 of Prolactin Levels

Male	**Screening**		**Week 2**		**Week 4**		**Week 6**		**Week 8**		**P Value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
	32.8	5.9	19.4	6.8	15.3	5.4	12.7	5.0	10.7	4.7	P<0.0001
Female	Screening		Week 2		Week 4		Week 6		Week 8		P Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
	48.3	5.9	34.6	9.6	28.5	8.8	24.8	8.7	20.8	8.6	P<0.0001

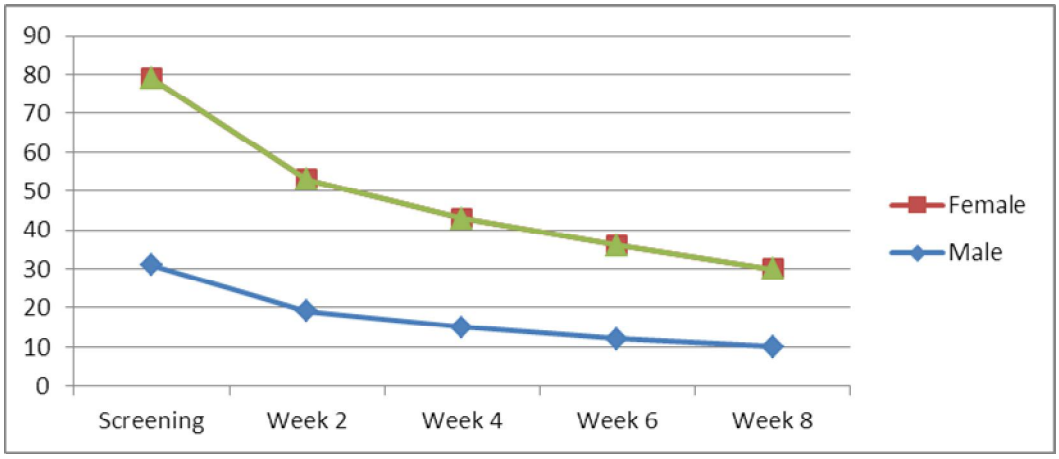

Figure –V : Line chart showing mean prolactin levels

Earlier studies have demonstrated Aripiprazole'sefficacy [15, 16] and the same was reflected in our findings. After augmenting of Aripiprazole, 93% of the patient's prolactin levels were normalized within 2- 8 weeks. However, Hyperprolactinemia occurred for one patient at week 8 visit. The patients reported adverse effects after adding the Aripiprazole into the treatment. The reported adverse effects were mild forms of insomnia and anxiety. The study was conducted only in subjects with schizophrenia and the maximum levels of prolactin was 60 ng/ml, Further studies with a longer study period and higher sample size along with other psychiatric disorders who are on Amisulpride, either higher doses or higher prolactin levels with a control sample may definitely be helpful to identify the Aripiprazole safety, tolerability, efficacy and any adverse events.

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