COMPARISON OF ARIPIPRAZOLE VERSUS HALOPERIDOL FOR THE TREATMENT OF CHILDHOOD AND ADOLESCENT NON-AFFECTIVE PSYCHOTIC DISORDERS

Banerjee Monideepa , Sinha Vinod K.

ABSTRACT

***Background**: Aripiprazole, a novel antipsychotic, is an effective and safe agent in psychotic disorders of adults but with limited evidence of use in pediatric patients. This study compares efficacy and safety of aripiprazole monotherapy with haloperidol for schizophrenia and related psychotic disorders in children and adolescents.*

***Methods and Materials:** Total 30 patients with ICD-10 DCR diagnosis of schizophrenia and acute psychotic disorders, were assigned to receive either aripiprazole (10-15 mg/day) or haloperidol (10-15mg/day) for four weeks, with each group containing 15 patients respectively. Primary outcome measure was Positive and Negative Syndrome Scale for Schizophrenia (PANSS) while secondary outcome measures were three PANSS subscales and Clinical Global Impressions-Severity of Illness (CGI-S). Assessments were done at baseline and then on weekly basis until endpoint. Extrapyramidal side effects and akathisia were rated weekly by Simpson-Angus Scale (SAS) and Barnes Akathisia Scale (BAS). Body weight and serum prolactin were measured and electrocardiogram recorded at baseline and at end point .*

***Results:** Endpoint improvement for the aripiprazole group was not significantly different from haloperidol group on PANSS total score, and PANSS positive and negative subscale scores. Haloperidol produced significantly greater improvement in PANSS general psychopathology subscale score and CGI-S score at endpoint. Aripiprazole produced significantly less extrapyramidal side effects and weight gain. Haloperidol produced significantly greater elevations in serum prolactin levels while QT (c) changes were nonsignificant in both groups.*

***Conclusions:** This trial shows that aripiprazole therapy was as efficacious as haloperidol in improving both positive and negative symptoms of psychotic disorders in children and adolescents but demonstrated better tolerability.*

Key words- ***aripiprazole, haloperidol, childhood, psychosis***

INTRODUCTION

Childhood and adolescent psychotic disorders are frequently devastating illnesses, characterized by disturbances in language, perception, cognition, affect, volition and socio- occupational functioning. Although estimates of prevalence of psychotic disorders in childhood vary, there is general consensus that they are uncommon[1]. In a study of first admission rates for various psychotic disorders, including schizophrenia, schizophreniform disorder, atypical psychosis and substance induced psychosis, reported prevalence rates were 1.8 per 10,000 in children under age of 13 years and 17.6 per 10,000 at age 18 years[2]. Conventionally, early onset schizophrenia is defined as onset before 18 years of age, and very early onset schizophrenia, defined as onset before age 13. It is estimated that 0.1 to 1.0 percent of all schizophrenic disorders present before age 10, with four percent occurring before age 15.Atypical antipsychotic agents are currently first choice drugs for treating childhood and adolescent onset psychoses. In a randomized double blind controlled trial of clozapine in early onset schizophrenia, the atypical antipsychotic was significantly superior to haloperidol, in 21 children and adolescents with early onset schizophrenia, on all outcome measures[3]. However serious adverse effects occurred in alarmingly high rates in clozapine treated group, including neutropenia and seizures. Another recent double blind controlled trial established olanzapine and risperidone monotherapy as equally efficacious as haloperidol, with shorter time to respond, in total 50 pediatric patients with schizophrenia and other psychotic disorders[4]. However, metabolic adverse effects are problematic for atypical agents, with high rates of hyperprolactinemia with risperidone[5] and weight gain with olanzapine[6] in pediatric patients.

Aripiprazole, a novel antipsychotic having unique action of dopamine system stabilization has been widely investigated in adult psychotic disorders and found to be as effective as haloperidol[7] and risperidone[8], in improving both positive and negative schizophrenic symptoms in randomized double- blind placebo controlled trials. However, it has been sparsely used in pediatric populations, with absence of any controlled trials. It has been found to be efficacious in pediatric patients in treatment of conduct disorder[9] and bipolar mania[10], in small open label trials and retrospective chart reviews.

Aripiprazole has been established to have a superior tolerability profile in adult psychotic patients, compared to conventional antipsychotics. A meta-analysis pooling data from five short term trials, involving total 1549 adult patients, revealed that aripiprazole produced extrapyramidal symptoms comparable to placebo and significantly lesser than haloperidol[11]. Aripiprazole has also not been associated with significant weight gain or QT(c) prolongation in controlled trials[12]. Aripiprazole is thus an attractive candidate for treatment of psychotic disorders in children and adolescents as it appears to have improved tolerability with less propensity for both extrapyramidal and metabolic side effects, which are particularly troublesome in this population and may compromise treatment adherence.

The primary intent of this open label comparison study was to evaluate the efficacy and tolerability of aripiprazole monotherapy compared with haloperidol in non-affective psychotic disorders in children and adolescents.

MATERIALS AND METHODS

This open label, active comparator controlled study of four weeks duration of active therapy was performed at a single site, a tertiary psychiatric referral hospital in India. The study protocol was approved by the institute's ethics committee, and as all patients were minors, legal guardians provided written informed consent before participation in any study related procedures. Each consecutively recruited patient was alternately allocated to receive haloperidol or aripiprazole, in a 1:1 schedule, with the first patient receiving haloperidol. The aripiprazole group received evening dose of 10mg/day for body weight below 50 kg and 15 mg/day for body weight above 50 kg. Similarly, haloperidol group received evening dose of 10 mg/day for body weight below 50 kg and 15mg/day for body weight above 50 kg.

All doses were fixed. Subjects who could not tolerate the minimal dose were discontinued from the study. Concomitant psychotropic medications were not permitted except for limited benzodiazepine use for agitation and insomnia (i.e. up to 6 mg/day lorazepam) and trihexyphenidyl (up to 6 mg/day) for extrapyramidal symptoms.

Subject eligibility included age _ 18 years, an ICD-10 DCR diagnosis of schizophrenia, schizoaffective disorder and acute transient psychotic disorder and drug naïve or drug free status for at least two weeks (for oral antipsychotics and six weeks for depot antipsychotics). Subjects with any comorbid neurological or psychiatric disorder were excluded. A total of 30 subjects participated in the study till the endpoint for four weeks with assignment into any of two treatment groups of 15 patients each.

A screening assessment (standard history, physical examination and laboratory profile) was conducted during the first visit, followed by baseline assessment on the same day. Thereafter, assessments were conducted weekly until week four. Body weight was recorded and electrocardiogram was performed at baseline and at study completion.

The primary efficacy measure was the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)[13] total score at endpoint. Secondary measures included the Clinical Global Impressions -Severity of illness (CGI-S) scale[14] and visitwise PANSS total scores.

Parkinsonism and akathisia were assessed weekly with the Simpson-Angus Scale[15] and the Barnes Akathisia Scale[16], while spontaneous reporting of other adverse events was recorded at each visit.

Statistical methods

Statistical analysis was done with the help of Statistical Package for Social Sciences version 10 (SPSS-10). Pearson chi-square (^{2}) tests were used for analysis of categorical variables. To avoid Type I error due to multiple comparisons, a series of general linear modeling repeat measures multivariate analyses of variance were performed to assess longitudinal group interactions and effects with PANSS total scores, PANSS individual subscale (positive, negative, general psychopathology) scores, CGI-S scores, Simpson Angus total scores, Barnes Akathisia Scale scores, body weight and QT (c) interval. Mauchly's test of sphericity assumptions were performed beforehand and the findings revealed significant deviation from sphericity assumptions. Consequently, Greenhouse-Geisser corrected F values were taken into consideration

only. Additonally, effect size (partial eta square), observed power and confidence interval were calculated for each comparison.

Response was defined as ≥30% decrease from baseline PANSS total score at endpoint.

All hypotheses were tested at a 2 tailed of 0.05.

RESULTS

A total of 30 subjects entered and completed the four week study with no discontinuations.

Table 1 gives the baseline demographic and clinical profile of the study sample by group assignment. Baseline demographics and baseline PANSS total and CGI-S scores were not statistically different among treatment groups.

Table 1 : Patient characteristics at baseline

Variables	Haloperidol (n = 15)	Aripiprazole (n = 15)
Gender, number female (%)	5 (33.3)	6 (40.0)
Age, mean years (SD)	15.33 (1.72)	15.33 (1.35)
Diagnosis number (%)		
Schizophrenia	8 (53.3)	9 (60.0)
Acute psychosis	7 (46.7)	6 (40.0)
Weight, mean kg (SD)	40.80 (8.56)	42.13 (9.93)
QTC interval, mean msec (SD)	405.33 (20.18)	404.13 (23.03)
Serum prolactin, mean ng/ml (SD)	13.71 ± 5.60	12.05 ± 4.28
Psychiatric profile, mean (SD)		
PANSS total	105.93 (19.80)	103.00 (14.91)
PANSS positive	28.47 (8.32)	30.00 (7.65)
PANSS negative	25.67 (10.37)	26.80 (9.07)
PANSS general psychopathology	51.80 (12.12)	46.20 (8.27)
CGI-S	6.27 (0.59)	6.07 (0.59)

At baseline, PANSS total scores were not significantly different between haloperidol group (mean 105.93±19.80) and aripiprazole group (mean 103.00±14.91) (p= 0.65). Also, there was no significant difference on any of the three subscale scores of positive syndrome, negative syndrome and general psychopathology.

PANSS total scores improved significantly from baseline to end point over four weeks in both haloperidol and aripiprazole groups showing significant treatment effect for both the groups. However, no significant treatment interactions could be observed for the PANSS total or subscale scores, except for the general psychopathology cluster. In the haloperidol group, general psychopathology subscale score improved significantly better than that in aripiprazole group (p=0.03; effect size=0.12; observed power=0.61) (Table 2).

	Variables	Pre (mean ± SD	Post (mean ± SD)	F (Greenhouse-Geisser correction)	P	Partial Eta squaared (Effect size)	Observed power
PANSS total	Haloperidol	105.93 ± 19.80	55.67 ± 18.63	1.28	0.28	0.04	0.24
	Aripiprazole	103.00 ± 14.91	60.00 ± 21.29				
PANSS positive scale	Haloperidol	28.47 ± 8.32	11.93 ± 7.20	0.07	0.90	0.00	0.06
	Aripiprazole	30.00 ± 7.65	12.40 ± 9.02				
PANSS negative scale	Haloperidol	25.67 ± 10.36	15.67 ± 7.48	0.47	0.60	0.16	0.12
	Aripiprazole	26.80 ± 9.07	17.33 ± 7.06				
PANSS general score	Haloperidol	51.80 ± 12.12	28.73 ± 7.37	3.83	0.03*	0.12	0.61
	Aripiprazole	46.20 ± 8.27	30.27 ± 9.58				

[* p 0.05(2- tailed)]

Subsequent analysis according to diagnostic groups revealed a differential effect of diagnosis on improvement of PANSS scores. Improvement over time was significantly better for patients with diagnosis of acute transient psychotic disorder than for patients with schizophrenia (p=0.00; effect size=0.23; observed power=0.93)

At baseline, there was no significant difference in CGI-S score between haloperidol group (mean 6.27±0.59) and aripiprazole group (mean 6.07±0.59). CGI-S scores improved significantly from baseline to endpoint over four weeks in both groups showing significant treatment effects for both groups. However, a significant treatment interaction was noted as, in the haloperidol group, CGI-S score improved significantly better than that in aripiprazole group (p=0.02; effect size=0.14; observed power=0.73) .

At week one, only one patient (6.7%) in haloperidol group and none (0%) in aripiprazole group were found to be responder. At week two, seven patients (46.7 %) in haloperidol group and six patients (40.0%) in aripiprazole group were responders. At week three, 12 patients (80.0%) in haloperidol group and 11 patients (73.3%) in aripiprazole group were responders. At endpoint, at week four, there were 12 responders (80.0%) and three nonresponders (20.0%) in both treatment groups. There were no significant group interactions with responder rates throughout the study period.

A significant interaction between extrapyramidal side effects and treatment group was noticed as parkinsonian side effects were more in haloperidol group than in aripiprazole group throughout study period of four weeks (p=0.00; effect size=0.40; observed power=1.00) (Table 3).

Table 3: Comparison of extrapyramidal symptom profile and serum prolactin levels across two groups

	Variables	Pre (mean ± SD	Post (mean ± SD)	F (Green house-Geisser correction)	P	Partial Eta squaared (Effect size)	Observed power
Simpson Angus total score	Haloperido	0.00 ± 0.00	10.20 ± 3.45	19.00	0.00**	0.40	1.00
	Aripiprazole	0.00 ± 0.00	2.20 ± 3.25				
Serum Prolactin level	Haloperidol	13.71 ± 5.60	41.82 ± 19.19	30.22	0.00**	0.52	1.00
	Aripiprazole	12.05 ± 4.28	10.57 ± 4.33				

[** p 0.005 (2-tailed)]

Barnes Akathisia Rating Score (Global assessment) increased from baseline to endpoint in both haloperidol and aripiprazole groups, with no significant interaction.

Haloperidol group also required significantly higher dose of trihexyphenidyl (mean dose 68.40 $\pm$ 19.72), while use of lorazepam was comparable in both groups.

At baseline, there was no significant difference in serum prolactin level between groups. At endpoint, a significant treatment interaction was noted, as serum prolactin level was significantly increased in haloperidol group compared to aripiprazole group (p-0.00; effect size=0.52; observe power=1.00). On the other hand, aripiprazole group showed a slight nonsignificant decrease in serum prolactin level from baseline to end point.

A significant interaction between body weight change and treatment group was noticed as weight gain was significantly more in haloperidol group than in aripiprazole group (p=0.04; effect size=0.14; observed power=0.54).

There was no significant group interaction in QT (c) interval over four weeks from baseline to endpoint.

DISCUSSION

To our knowledge, this is the first prospective controlled trial of aripiprazole in pediatric patients with schizophrenia and other non affective psychosis. In this trial, both aripiprazole and haloperidol demonstrated significant effectiveness for overall symptom improvement as reflected by PANSS total scores as well as positive and negative subscale scores with no significant between group interactions.

However, haloperidol produced significantly better improvement than aripiprazole in CGI-S score and PANSS general psychopathology subscale score at endpoint. On the other hand, aripiprazole produced significantly less extrapyramidal symptoms and weight gain, than haloperidol.

Similar to results in previous trials in adult psychotic patients, aripiprazole produced improvement comparable to haloperidol in both positive and negative symptoms in early onset psychoses, as expected from pharmacodynamic profile of partial D2 receptor agonism[7]. At low dopamine levels, it stimulates dopamine receptors and at high dopamine levels, inhibition of dopamine activity occurs. Since positive symptoms are thought to be caused by hyperdopaminergic activity in the mesolimbic tract and negative symptoms by hypodopaminergic activity in the mesocortical tract, aripiprazole can produce improvement in both syndrome domains.

However, better improvement in general psychopathology scores with haloperidol may be due to the fact that haloperidol is more sedating and less activating due to higher D2 receptor antagonism while aripiprazole as a partial D2 receptor agonist is more activating, at times producing nonspecific de novo side effects like insomnia, agitation, anxiety and tension[12] which may adversely affect general psychopathology score outcomes. There are emerging case reports of worsening psychosis, increased agitation and even emergent suicidality with use of aripiprazole in adults[17,18].

Decreased risk of extrapyramidal symptoms is consistent with pharmacodynamic profile of aripiprazole as D2 receptor partial agonist, while with haloperidol, a high potency D2 antagonist, dopaminergic neurotransmission is blocked in nigrostriatal tract, causing pseudo-parkinsonism. In contrast, aripiprazole acts as dopamine agonist in conditions of low, endogenous dopamine activity, preventing development of hypodopaminergia in nigrostriatal region. This low propensity for parkinsonian side effects is similar to rates reported in adult studies, which were comparable to placebo and significantly less than haloperidol[11].

As a modest H1 receptor antagonist, aripiprazole is associated with minimal weight changes and has even been found to cause mean weight loss from baseline in some trials[19].

In the current study, aripiprazole group demonstrated slight but nonsignificant reduction in serum prolactin levels from baseline to endpoint, while serum prolactin was significantly elevated over baseline with haloperidol treatment. In fact, data from adult studies indicate that aripiprazole treatment frequently produces reductions from baseline prolactin levels compared to placebo (-56.5% versus 0%) while haloperidol is associated with very significant prolactin elevations (120% over baseline)

This study has several limitations. First, sample size is very small, mostly due to rarity of diagnosis of non affective psychotic disorders in pediatric patients. This is borne out by similarly inadequate sample size in all controlled trials, examining atypical antipsychotic agents like clozapine and olanzapine[3]. Secondly, both treatment groups had heterogenous diagnostic composition, namely schizophrenia and acute transient psychotic disorder. This factor may have contributed to overestimation of clinical improvement in treatment groups, as acute psychotic patients improved better and faster than schizophrenic patients. Thirdly, this is a nonrandomized open label study lacking blinding, which may contribute to selection and assessment bias. Thus, results of this study must be considered as purely preliminary and exploratory, making generalizations difficult.

Lastly, there is lack of placebo control, a requisite part of a pharmacotherapy trial, which was not possible due to ethical constraints. However, use of haloperidol as an active comparator, which has already been established as clearly more efficacious than placebo in a previous randomized controlled study in this patient population[20], has alleviated this problem to some extent.

In summary, this preliminary study indicated that aripiprazole was equally efficacious as haloperidol in improving overall symptoms as well as positive and negative syndrome domains of schizophrenia, while offering better tolerability with respect to extrapyramidal symptoms and body weight, and reducing the need for concomitant antiparkinsonian agents.

REFERENCES

1. Volkmar, F.R. (1996). Childhood and adolescent psychosis: a review of past ten years. J Am Acad Child Adolesc Psychiatry 1996; 35 (7): 843-851.
2. Gilberg C, Wahlstrom J, Forsman A, et al. Teenage psychosis-epidemiology, classification and reduced optimality in the pre-, peri- and neonatal periods. J Child Psychol Psychiatry 1986; 27: 87-98.
3. Kumra S, Frazier J A, Jacobsen L K, et al. Childhood-onset schizophrenia: a double blind clozapine-haloperidol comparison. Arch Gen Psych 1996; 53: 1090-1097.
4. Sikich L, Hamer, R M, Bashford, R A, et al. A pilot study of risperidone, olanzapine and haloperidol in psychotic youth: a double blind, randomized eight week trial. Neuropsychopharmacology 2004; 29:33-145.
5. Findling, R L, Kusumakar V, Daneman D, et al. Prolactin levels during longterm risperidone treatment in children and adolescents. J Clin Psychiatry 2003; 64: 1362 – 1369.
6. Ratzoni G, Gothelf D, Brand-Gothelf D, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. J Am Acad Child Adolesc Psychiatry 2002; 41 (3): 337-343.
7. Kane J M, Ingenito G, Ali M. Efficacy of aripiprazole in psychotic disorders: comparison with haloperidol and placebo. Schizophr Res 2000; 41: 39-46.
8. Potkin, S.G., Saha, A., Kujawa M, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone versus placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psych 2003; 60: 681-690.
9. Findling R L, Blumer J L, Kauffman R, et al. Pharmacokinetic effects of aripiprazole in conduct disorder. Eur Neuropsychopharmacol 2005; 13: 34-40.
10. Barzman D H, Delbello M, Kowatch R, et al. The effectiveness and tolerability of aripiprazole for pediatric bipolar disorder: a retrospective chart review. J Child Adolesc Psychopharmacol 2004; 14: 539-600.
11. Marder S R, McQuade R D, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term placebo controlled trials. Schizophr Res 2003; 61: 123-136.
12. Keck P E, McElroy S L. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. Expert Opin Investig Drugs 2003; 12 (4): 655-662.
13. Kay S R, Opler L A, Lindenmayer J P. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261-276.
14. Guy W. ECDEU assessment manual for psychopharmacology 1976. Washington DC, U.S. Department of Health Education and Welfare.
15. Simpson G M, Angus J W S. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970; 212 (Suppl 44): 11-19.

16. Barnes T R E. A rating scale for drug induced akathisia. British Journal of Psychiatry 1989; 154: 672-676.

17. Barnas M E, Hussain N, Petrides G. Treatment emergent psychosis with aripiprazole. J Clin Psychiatry 2005; 66: 1339.

18. Holzer K, Eap C B. Aripiprazole and suicidality. Int Clin Psychopharmacology 2006; 21: 125-126.

19. McQuade R, Stock E, Marcus R, et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double blind study. J Clin Psychiatry 2004; 65 (Suppl 18): 47-56.

20. Spencer K S, Campbell M. Children with schizophrenia: diagnosis, phenomenology and pharmacotherapy. Schizophr Bull 1994; 20 (4): 713-725.

Authors :

1. **Dr. Monideepa Banerjee,** D.P.M., M.D.
Assistant Professor of Psychiatry,
KPC Medical College and Hospital,
Kolkata, West Bengal.

2. **Dr. Vinod K. Sinha,** D.P.M., M.D.,
Professor of Psychiatry,
Central Institute of Psychiatry,
Ranchi, Jharkhand.

Address for correspondence:
Dr. Monideepa Banerjee, D.P.M., M.D.,
Assistant Professor of Psychiatry,
KPC Medical College and Hospital, Kolkata,
Jadavpur, Kolkata,West Bengal, India,
Pin-700068.
Mobile- 9831110200
E-mail- monideepa.banerjee@yahoo.in

❖❖❖