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ORIGINAL PAPER

A Double-blind Placebo Controlled Trial of Piracetam Added to Risperidone in Patients with Autistic Disorder

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Abstract It has been reported that autism is a hypoglutamatergic disorder. Therefore, it was of interest to assess the efficacy of piracetam, a positive modulator of AMPA-sensitive glutamate receptors in autistic disorder. About 40 children between the ages three and 11 years (inclusive) with a DSM IV clinical diagnosis of autism and who were outpatients from a specialty clinic for children were recruited. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated to piracetam + risperidone (Group A) or placebo + risperidone (Group B) for a 10-week, double-blind, placebo-controlled study. The dose of risperidone was titrated up to 2 mg/day for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. The dose of piracetam was titrated up to 800 mg/day. Patients were assessed at baseline and after 2, 4, 6, 8 and 10 weeks of starting medication. The measure of the outcome was the Aberrant Behavior Checklist-Community (ABC-C) Rating Scale (total score). The ABC-C Rating Scale scores improved with piracetam. The difference between the two protocols was significant as indicated by the effect of group, the between subjects factor ($F = 5.85$, d.f. = 1, $P = 0.02$). The changes at the endpoint compared with baseline were: –11.90 ± 3.79 (mean ± SD) and –5.15 ± 3.04 for group A and B respectively. A significant difference was observed on the change in scores in the

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ABC-C Rating Scale in week 10 compared with baseline in the two groups ($t = 6.017$, d.f. = 38, $P < 0.0001$). The results suggest that a combination of atypical antipsychotic medications and a glutamate agent such as piracetam, might have increase synergistic effects in the treatment of autism.

Keywords AMPA · Autism · Glutamate · Piracetam

Introduction

Autism is a complex neurodevelopmental disorder that forms part of a spectrum of related disorders referred to as Autism Spectrum Disorders and characterized by pattern of delay and differences in the development of social, communication, and cognitive skills; a markedly restricted repertoire of activities and interest; and repeated and restricted patterns of movement [1–3]. Although research studies have generated much evidence to suggest that genetic and neurobiological factors play important role in the pathogenesis of autism, its etiology is still unclear [1, 3, 4]. The prevalence of autism is currently estimated at 5 in 1000 children for the full spectrum of autistic disorders. Familial recurrence of the disorder is 100-fold higher than in the general population [2].

Antipsychotic drugs are among the most commonly used psychopharmacological agents for treatment of autism [5]. However, conventional types may have undesirable side effects such as dystonia and tardive dyskinesea that limit their clinical use [6]. On the other hand, second generation antipsychotic medications, which produce a greatly reduced risk of extrapyramidal symptoms are in the front line of psychopharmacological treatments [7]. Nevertheless, there are some concerns regarding metabolic disorders and atypical antipsychotics.

In addition to serotonergic abnormalities, the strongest evidence implicates the glutamatergic and GABAergic systems are important biochemical factors in autism [8–12]. One current hypothesis is that autism is a hypoglutamatergic disorder [13]. This hypothesis is based on neuroanatomical and neuroimaging studies and supported by similarities between symptoms produced by N-methyl-D-aspartate (NMDA) antagonists in healthy subjects and those seen in autism [14, 15]. If there is deficient glutamatergic transmission in autism, the most logical treatment would of course be a glutamatergic agent. In the treatment of schizophrenia, that has many similarities with autism either D-cycloserine (glycine agonist) or piracetam showed promising results [16, 17]. Indeed, autism and schizophrenia have some similarities regarding the role of serotonin and glutamate in their pathophysiology. Piracetam is a member of the nootropic class of drugs, which have cognition enhancing effects, it appears to modulate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acids)-sensitive glutamate receptors positively and has been used in many countries in the management of dementia [18–20]. Although its mode of action is not certain, it is said to protect the cerebral cortex against hypoxia and has been used following trauma or surgery and in a variety disorders including senile dementia and behavioral disorders in children [18–20]. In addition, it is used in the treatment of dyslexia and some type of myoclonus in adults [18–20]. Indeed. Piracetam is the most studied nootropic in children.

With these points in mind, in this 10-week double-blind, placebo controlled trial, we assessed the effects of piracetam plus risperidone in the treatment of autistic disorder. To our knowledge, this study is the first double-blind and placebo-controlled clinical trial assessing the adjunctive role of piracetam in the management of autism.

Method

Trial Setting

This was a 10-week, parallel group, placebo-controlled trial undertaken in children outpatient clinic of Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran during January 2004–January 2006.

Participants

Participants were children and adolescents between the ages of 3 and 11 years (inclusive) with a DSM IV clinical diagnosis of autism and who were outpatients from a specialty clinic for children at Roozbeh Psychiatric Teaching Hospital [21]. Patients were referred by pediatricians, family physicians and parents from different parts of Tehran. The patients presented with a chief complaint of severely disruptive symptoms related to autistic disorder. The diagnosis of autism was confirmed by a child psychiatrist (M.R. Mohammadi) based on behavioral observation of the child and semistructured interview with the parent, a score of ≥6 on the DSM IV diagnosis criteria for autism and clinical judgment. Children were excluded if they had previously received neuroleptics or any psychotropic drug treatment 6 months prior to recruitment or having significant active medical problem. Children with severe or profound mental retardation in whom a definitive diagnosis of autism could not be made were excluded. IQ was assessed by clinical judgment. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by ethics committee at Tehran University of Medical Sciences [22]. Written informed consents were obtained before entering into the study from the parents of patients.

Study Design

About 40 patients were randomly assigned equally to either piracetam + risperidone (Group A) or placebo + risperidone (Group B) for a 10-week, double-blind, placebo-controlled study. All patients completed the trial. The dose of risperdone was titrated up to 2 mg/day as fixed dose (0.5 mg starting dosage with 0.5 mg increments in weekly dosage for the first three weeks) for children between 10 and 40 kg and 3 mg/day (fixed dose) for children weighting above 40 kg. The dose of piracetam was titrated up to 800 mg/day (200 mg/day starting dosage with 200 mg increments every two days). Placebo was prepared identical in appearance (shape, size, color, and taste) and was dispensed by the investigational drug pharmacist. The patients did not receive any other psychosocial therapies during the trial.

Outcome

The measure of the outcome was the Aberrant Behavior Checklist-Community (ABC-C) (total score) [23]. ABC-C is an empirically derived psychometric instrument designed to rate the presence and severity of maladaptive behaviors within the learning disabilities population, based on an earlier version of the ABC. The checklist was developed from

problem behaviors known to occur with some frequency in moderate to severe learning disabled individuals (lethargy, hyperactivity, inappropriate speech, irritability and stereotypy). The rater followed standardized instructions in the use of the ABC-C Rating Scale. The mean decrease in the ABC-C Rating Scale score from baseline was used as the main outcome measure for response to autism treatment. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) [24]. Patients were randomized to receive piracetam or placebo in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until the point of data analysis. Each child was rated at baseline and at week 2, week 4, week 6, week 8 and week 10 (endpoint) by ABC-C Rating Scale. Throughout the study, the person who administrated the medications, the rater and the patients were blind to assignments. Patients were assessed by a third-year resident of psychiatry (H. Tajdar) with help and information that patients' parents gave him. He was trained by child psychiatrist in the use of the translated versions of these rating scales.

Side Effects

Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry during weeks 1, 2, 4, 6, 8 and 10. This was done through questions of resident of psychiatry.

Statistical Analysis

A two-way repeated measures analysis of variance was used. The two groups were considered as a between-subjects factor (group) and the six measurements during treatment as a within-subjects factor (time) in the analyses. These were carried out for the ABC-C Rating Scale scores. In addition, a one-way repeated measures analysis of variance with a two-tailed post hoc Tukey mean comparison tests was performed on the change of the ABC-C Rating Scale scores from baseline. To compare the reduction in score of the ABC-C Rating Scale at week 10 compared with baseline, an unpaired two-sided Student's t-test was used. Results are presented as mean ± SD differences and were considered significant at $P < 0.05$. To compare the baseline data, differences in the frequency of side effects and frequency of extrapyramidal symptoms with the two treatments were assessed using Fisher's exact test. With a Type 1 error $\alpha = 0.05$, and $\beta = 0.2$, and a final difference in score between the two groups of at least score 5 on the ABC-C rating scale, the sample size necessary was calculated to be at least 15 patients in each group.

Results

About 58 patients were screened for the study. About 18 patients were excluded from the study because they were receiving other psychotropic medications or had other significant active medical problems such as epilepsy. Forty patients were randomized to trial medication (Fig. 1.). No significant differences were identified between patients randomly assigned to the group A or B condition with regard to basic demographic data including age gender and weight (Table 1). All patients completed the trial and there were no missing data.

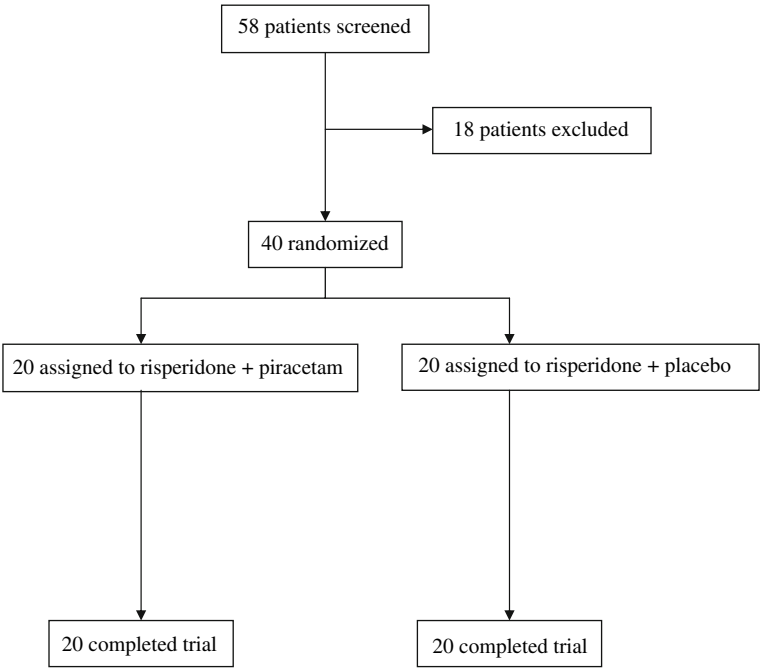

Fig. 1 Trial profile

Piracetam Versus Placebo: The ABC-C Rating Scale

The mean ± SD scores of the two groups of patients are shown in Fig. 2. There were no significant differences between the two groups at baseline (week 0) on the ABC-C Rating Scale (total score) ($t = 0.37$, d.f. = 38, $P = 0.70$) [23.15 ± 5.80 and 24.00 ± 8.25

Table 1 Characteristics of patients

	Risperidone + piracetam	Risperidone + placebo	*P*
Age (mean ± SD)	6.90 ± 1.86 [11 (max) & 3 (min)]	6.75 ± 1.80 [11 (max) & 3 (min)]	0.44
Age distribution	Age 3 (1 Child)	Age 3 (1 Child)	NS
	Age 5 (4 Children)	Age 4 (1 Child)	
	Age 6 (4 Children)	Age 5 (2 Children)	
	Age 7 (2 Children)	Age 6 (5 Children)	
	Age 8 (6 Children)	Age 7 (4 Children)	
	Age 9 (2 Children)	Age 8 (5 Children)	
	Age 11 (1 Child)	Age 9 (1 Child)	
		Age 11 (1 Child)	
Gender	Boy: 16, Girl: 4	Boy: 14, Girl: 6	0.77
Weight (mean ± SD)	24.55 ± 5.41 (kg)	25.25 ± 6.25 (kg)	0.70
History of previous	Eight patients: risperidone	Ten patients: risperidone	NS
Medications	Four patients: haloperidol	Three patients: haloperidol	

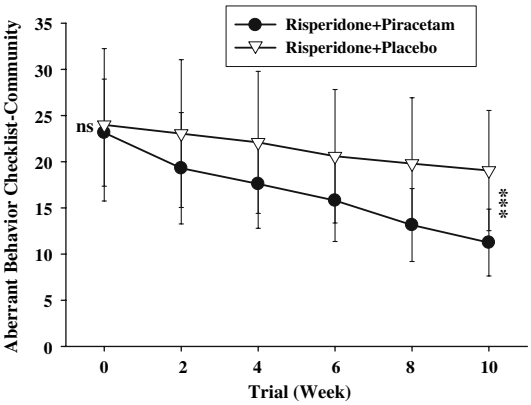

Fig. 2 Mean ± SD of the two protocols on the Aberrant Behavior Checklist-Community (ABC-C) Rating Scale (total score). ns = non-significant and *** <0.001

(mean ± SD) for group A and B respectively]. The behavior of the two treatments was not homogeneous across the time (groups-by-time interaction, Greenhouse–Geisser correction; $F = 24.57$, d.f. = 1.93, $P < 0.0001$). The difference between the two protocols was significant as indicated by the effect of group, the between subjects factor ($F = 5.85$, d.f. = 1, $P = 0.02$). In addition, a one-way repeated measures analysis of variance showed a significant effect of piracetam on the ABC-C Rating Scale (total score) ($P < 0001$). In the piracetam group post hoc comparisons showed a significant change from week 4 compared to baseline on the ABC-C Rating Scale. The difference between the two protocols was significant at the endpoint (week 10) ($t = 4.67$, d.f = 38, $P < 0.0001$). The changes at the endpoint compared with baseline were: –11.90 ± 3.79 (mean ± SD) and –5.15 ± 3.04 for group A and B respectively. A significant difference was observed on the change in scores in the ABC-C Rating Scale (total score) in week 10 compared with baseline in the two groups ($t = 6.017$, d.f. = 38, $P < 0.0001$).

Extrapyramidal Symptoms Rating Scale

The extrapyramidal symptoms were observed in six and eight patients in the piracetam and placebo groups respectively. No significant difference was observed between the two groups ($P = 0.74$).

Clinical Complications and Side Effects

Eight side effects were observed over the trial out of 25 side effects that the checklist included them. The difference between the two groups in the frequency of side effects was not significant (Table 2).

Discussion

Autistic disorder is a pervasive developmental disorder whose core symptoms are a qualitative impairment in social interaction and communication and restricted repetitive and stereotyped patterns of behavior, interests, and activities [2]. Drug treatment has a

Table 2 Number of patients with side effects

Side Effects	Risperidone + piracetam	Risperidone + placebo	*P*
Constipation	4	3	NS
Nervousness	1	2	NS
Day time drowsiness	7	9	NS
Morning drowsiness	11	8	NS
Increased appetite	7	6	NS
Dry mouth	4	3	NS
Fatigue	5	3	NS
Loss of appetite	1	1	NS

place in reducing symptoms and can enhance the quality of life of children and adolescents and their families [7]. Nevertheless, as the etiology of autism is poorly understood [11], drug treatment is not a magic bullet *per se*. Drugs affecting the glutamate receptors have been investigated as therapeutic agents in several neuropsychiatric disorders including autism [25]. It has been reported that autism is a hypoglutamatergic disorder on the basis of NMDA antagonist effects in humans and mice [13, 14]. Therefore, it was of interest to assess the efficacy of piracetam, a positive modulator of AMPA-sensitive glutamate receptors in autistic disorder [20]. The present study shows that the ABC-C Rating Scale scores improved with piracetam over this 10-week, double-blind and placebo-controlled trial. The efficacy of piracetam in patients with autistic disorder seems to support the hypoglutamatergic hypothesis of the disease.

In addition, no severe side effects were observed with either treatments and there was no significant difference in the frequency of side effects and extrapyramidal adverse effects. Nevertheless, it may be possible that the study was relatively small to determine differences in side-effect rates and it should be considered as a limitation of this study. The results are concordant with several recent studies that indicate similarities between symptoms of autism and schizophrenia. It was reported that both D-cycloserine and piracetam (glutamate agents) can reduce symptoms of schizophrenia [16, 17]. Furthermore, D-cycloserine, an antibiotic that is a partial agonist at the glycine binding site of NMDA glutamate receptors, has been proposed as a treatment of autism [26]. Indeed, Posey et al (2004) published a 2-week single –blind placebo lead-in phase to treatment with three different doses of D-cycloserine. On the highest dose, patients had statistically significant improvement in social withdrawal [26]. There is an explanation that may account for this phenomenon. The reduction in global levels of glutamate signaling might occur by over activation of excitatory receptors on cortical GABA interneurones, such as dose of 5-HT2A receptor subtype, leading to pronounced depression of the excitatory glutamatergic circuitry. This possibly supported by the relative efficacy of combined treatment with partial glutamate agonists and 5-HT2A receptor antagonists such risperidone in autism as well as in hypoglutamatergic animal models [26].

The limitations of the present study, including the small number of patients and the short period of follow-up requires that the results be confirmed in larger randomized controlled trials. In addition, only behavior problems or maladaptive behaviors were assessed in this trial and we recommend further studies regarding adaptive functioning. Although, piracetam–nootropics are among the toxicologically safest drugs for children and adolescents [27, 28], the rational for ploypharmacy is limited to severe associated

symptoms including aggression, severe temper tantrums, self injuries behaviors, hyperactivity and stereotypies. The results of this study suggest possible benefit of treatment with glutamate agents. This goal can be achieved by ampaknies group such as piracetam. Therefore, other agents from this family should be investigated in the treatment of autism. In addition, from a scientific viewpoint, the therapeutic effects of piracetam without an additional neuroleptic drug would be more interesting. However, since atypical antipsychotics are relatively effective in the treatment of autism, our national ethic committees would not approve a study with piracetam as the only drug for autistic patients. In conclusion, the results suggest that a combination of atypical antipsychotic medications and a glutamate agent such as piracetam, might have increase synergistic effects in treatment of behavioral problems of children with autism.

Summary

One current hypothesis is that autism is a hypoglutamatergic disorder. If there is deficient glutamatergic transmission in autism, the most logical treatment would of course be a glutamatergic agent. Piracetam is a member of the nootropic class of drugs, which have cognition enhancing effects, it appears to modulate AMPA- sensitive glutamate receptors positively and has been used in many countries in the management of dementia. In this 10-week double-blind, placebo controlled trial, we assessed the effects of piracetam plus risperidone in the treatment of autistic disorder. The present study shows that the ABC-C Rating Scale scores improved with piracetam over this 10-week, double-blind and placebo-controlled trial. The efficacy of piracetam in patients with autistic disorder seems to support the hypoglutamatergic hypothesis of the disease. The results suggest that a combination of atypical antipsychotic medications and a glutamate agent such as piracetam, might have increase synergistic effects in the treatment of autism.

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