Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial

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Abstract

Autism is a neurodevelopmental disorder that causes significant impairment in socialization and communication. It is also associated with ritualistic and stereotypical behaviour. Recent studies propose both hyper-and hypoglutamatergic ideologies for autism. The objective of this study was to assess the effects of memantine plus risperidone in the treatment of children with autism. Children with autism were randomly allocated to risperidone plus memantine or placebo plus risperidone for a 10-wk, double-blind, placebo-controlled study. The dose of risperidone was titrated up to 3 mg/d and memantine was titrated to 20 mg/d. Children were assessed at baseline and after 2, 4, 6, 8 and 10 wk of starting medication protocol. The primary outcome measure was the irritability subscale of Aberrant Behavior Checklist–Community (ABC-C). Difference between the two treatment arms was significant as the group that received memantine had greater reduction in ABC-C subscale scores for irritability, stereotypic behaviour and hyperactivity. Eight side-effects were observed over the trial, out of the 25 side-effects that the checklist included. The difference between the two groups in the frequency of side-effects was not significant. The present study suggests that memantine may be a potential adjunctive treatment strategy for autism and it was generally well tolerated. This trial is registered with the Iranian Clinical Trials Registry (IRCTT11389011556N10; www.irct.ir)

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Introduction

Autistic disorder is one of a group of neurodevelopmental disorders known as pervasive developmental disorders (PDDs). These disorders are characterized by three core deficits: impaired communication; impaired reciprocal social interaction; restricted, repetitive and stereotypic patterns of behaviours or interests. Autism has also been referred to as autism spectrum disorder (ASD), because the severity and manifestation of the symptoms vary widely, ranging from modest social impairment to severe developmental and behavioural challenges. ASDs affect approximately one in 88 children in the United States. ASDs are usually lifelong chronic disabilities (Mohammadi & Akhondzadeh, 2007). These core symptoms are frequent targets of medical, behavioural and educational interventions. Associated symptoms such as hyperactivity, anxiety, aggression, insomnia and gastrointestinal symptoms are also common in ASDs and are frequent targets of both conventional treatments and complementary and alternative medicine therapies (Mohammadi & Akhondzadeh, 2007).

At present, there is no cure for the core symptoms of autism. However, several groups of medications, including atypical antipsychotics, have been used to treat associated behavioural problems such as aggression and self-injury (Nazeer, 2011). Pharmacological intervention may aid in the implementation of behavioural approaches by reducing interfering symptoms associated, such as hyperactivity and irritability (McPheeters et al. 2011). Glutamate, the major excitatory neurotransmitter, is highly concentrated throughout the brain and is crucial to neuronal plasticity and the maintenance of cognitive functioning (Carlson, 2012). However, excess glutamate has been shown to be a potent neurotoxin that leads to neuronal cell death and is deemed to play a role in the pathophysiology of some neuropsychiatric disorders.
Recently, a hyperglutamatergic hypothesis of autism was proposed based on evidence of hyperglutamatergia in the brain of individuals with autism (Fatemi et al. 2011). This hypothesis is proposed from several lines of evidence. For example, the levels of rate-limiting enzymes glutamate acid decarboxylase 65 and 67 were reduced in the brains of autistic subjects (Fatemi et al. 2002). In addition, increased gliosis has been found in the brains of autistic subjects, suggesting that increases in the number of glial cells may contribute to increases in glutamate availability in the brain (Laurence & Fatemi, 2005). It has been reported that infantile autism is a hypoglutamatergic disorder. This hypothesis is based on two findings: (1) neuroanatomical and neuroimaging studies indicating aberrations in brain regions that are rich in glutamate neurons; (2) similarities between studies indicating aberrations in brain regions that are rich in glutamate neurons; and baseline (Aman et al. 1985). In addition, diagnosis was corroborated by the Autism Diagnostic Interview-Revised, which was administered by an experienced child psychiatrist (Lord et al. 1994). There were no regional restrictions for participants as they were referred by paediatricians, family physicians and parents from different parts of Tehran and different regions of Iran. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder and most sought medical interventions. The exclusion criteria were concomitant schizophrenic or psychotic disorders, having a history of drug or alcohol abuse or tardive dyskinesia, having received any antipsychotic drug treatments 6 months prior to entry due to other reasons (such as discontinuation of treatment by parents). Severe mental retardation, which makes the diagnosis of autism inconclusive (based on the clinical judgement of a child psychiatrist), was also an exclusion criterion. Potential subjects were excluded if they had previously received memantine. In addition, children with active clinical seizures were excluded. The protocol was approved by the IRB of TUMS (Grant No: 6964). The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and was approved by the ethics committee at TUMS. Written informed consents were obtained from the parents of the children before entering the trial. This trial is registered with the Iranian Clinical Trials Registry (IRCT1138901151556N10; www.irct.ir).

Method

This was a 10-wk, parallel group, placebo-controlled clinical trial assessing the adjunctive role of memantine in the management of autism.

Participants

Children were considered for participation in the project if they were aged between 4 and 12 yr and met DSM IV-TR criteria for diagnosis of autism (APA, 2000). Criteria for the diagnosis of autism as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association were assessed for each child in order to provide documentation of the diagnosis before study entry. The diagnosis was confirmed by a child psychiatrist (M.R. Mohammadi) based on behavioural observation of the child and semi-structured interview with the parents with six or more DSM-IV-TR criteria deemed necessary for a diagnosis of autism. The children had to have an Aberrant Behavior Checklist–Community (ABC-C) Irritability subscale score of $\geq$ 12 at screening and baseline (Aman et al. 1985). Severe mental retardation, which makes the diagnosis of autism inconclusive (based on the clinical judgement of a child psychiatrist), was also an exclusion criterion. Potential subjects were excluded if they had previously received memantine. In addition, children with active clinical seizures were excluded. The protocol was approved by the IRB of TUMS (Grant No: 6964). The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and was approved by the ethics committee at TUMS. Written informed consents were obtained from the parents of the children before entering the trial. This trial is registered with the Iranian Clinical Trials Registry (IRCT1138901151556N10; www.irct.ir).

Study design

Forty patients were randomly assigned to two groups of equal size of either memantine (Ebixa; Lundbeck A/S, Denmark) plus risperidone (Risperdal; Janssen Pharmaceuticals, Belgium) or placebo plus risperidone for 10 wk. The dose of risperidone (0.5 mg tablets) was titrated up to 2 mg/d (starting dose of 0.5 mg with subsequent dose increase in 0.5 mg increments in the weekly dosage for the first 3 wk) for children weighing between 10 and 40 kg and 3 mg/d for children weighing $>40$ kg. Participants were started on 5 mg/d memantine (5 mg caplets) once daily, taken either whole or crushed. This was titrated up or down in 5-mg increments every week. These children were gradually titrated up to a maximum...
dose of 15 mg/d for children weighing between 10 and 40 kg and 20 mg/d for children weighing >40 kg. Placebo was identical in appearance (shape, size, colour and taste) and was dispensed by the investigational drug pharmacist. We started both drugs (memantine and risperidone) simultaneously. Although some patients had received psychosocial interventions before entry, they did not receive any psychosocial therapies during the course of the trial.

**Outcome**

The primary outcome measure was the irritability subscale of ABC-C (Aman et al. 1985). ABC-C is a 58-item tool to evaluate the existence and severity of disruptive behaviours and designated for rating the individuals with developmental disabilities. It assesses five types of behavioural abnormalities, three of which address the core deficits of autism (lethargy/social withdrawal, stereotypic behaviour and inappropriate speech) and the remaining two appraise the associated disturbances (irritability, hyperactivity/non-compliance). The ABC-C rating scale has been used in several studies in Iranian populations (Akhondzadeh et al. 2004, 2010; Asadabadi et al. 2012; Rezaei et al. 2010). The rater followed standardized instructions when using the ABC-C rating scale. The mean decrease in the ABC-C irritability subscale score from baseline was used as the main outcome measure for response to treatment. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (Chouinard et al. 1980). Patients were randomized to receive memantine or placebo in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until data analysis. Each child was rated at baseline and at weeks 2, 4, 6, 8 and 10 (end-point) by the ABC-C rating scale. Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments. Patients were assessed by a resident of psychiatry (M. S.) with input from the children’s parents (behaviour was rated by M. S. and their parents every 2 wk). M. S. was trained by a child psychiatrist in the use of the translated versions of ABC-C rating scales and she completed the ABC-C after interviewing study participants’ parents.

**Side-effects**

Side-effects were recorded every 2 wk, starting at the second week of the trial using a checklist administered by a medical student. Entries were based on responses from parents. The behaviour appraisals and side-effects were completed by independent raters.

**Statistical analysis**

Results are presented as mean ± S.D. differences and were considered significant at \( p \leq 0.05 \). A two-way repeated measures analysis of variance was used. The two groups were considered as a between subjects factor (group) and the five measurements during treatment were considered as a within-subjects factor (time) in the analyses. To compare the baseline data, differences in 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 5 units on the ABC-C irritability subscale, the sample size necessary was calculated to be at least 15 patients in each group.

**Results**

Forty children were randomized to the trial. Patients of both groups (risperidone + memantine vs. risperidone + placebo) were statistically identical according to basic demographic data, including age and gender (Fig. 1 and Table 1). All children completed the trial and there were no missing data.

**Memantine vs. placebo: irritability subscale**

The mean (S.D.) scores of the two groups of patients are shown in Table 2. The difference between the two treatments was significant, as indicated by the effect of groups \( \times \) time interaction \( (F = 21.48, \text{d.f.} = 1.78, p \leq 0.001) \).

**Memantine vs. placebo: lethargy/social withdrawal subscale**

The mean (S.D.) scores of the two groups of patients are shown in Table 2. The difference between the two treatments was not significant, as indicated by the effect of groups \( \times \) time interaction \( (F = 2.56, \text{d.f.} = 1.43, p = 0.10) \).

**Memantine vs. placebo: stereotypic behaviour subscale**

The mean (S.D.) scores of the two groups of patients are shown in Table 2. The difference between the two treatments was significant, as indicated by the effect of groups \( \times \) time interaction \( (F = 30.42, \text{d.f.} = 1.53, p \leq 0.01) \).

**Memantine vs. placebo: hyperactivity/non-compliance subscale**

The mean (S.D.) scores of the two groups of patients are shown in Table 2. The difference between the two treatments was significant, as indicated by the effect of groups \( \times \) time interaction \( (F = 153.50, \text{d.f.} = 1.53, p \leq 0.01) \).

**Memantine vs. placebo: inappropriate speech subscale**

The mean (S.D.) scores of the two groups of patients are shown in Table 2. The difference between the two protocols was not significant, as indicated by the effect of groups \( \times \) time interaction \( (F = 2.04, \text{d.f.} = 2.20, p = 0.13) \).
Extrapyramidal symptoms rating scale
Extrapyramidal symptoms were observed in five and six patients in the memantine and placebo groups respectively. No significant difference was observed between the two groups in the frequency of side-effects was not significant (Table 3 and Supplementary Table S1).

Clinical complications and side-effects
Eight side-effects were observed over the trial, out of the 25 side-effects that the checklist included. The difference between the two groups in the frequency of side-effects was not significant (Table 3 and Supplementary Table S1).

Discussion
Over the last two decades, there has been significant progress in the development of treatment strategies for both core and associated symptoms of ASD (Currenti, 2010; Nazeer, 2001). Several lines of evidence support...
the hypothesis that abnormalities in glutamatergic neurotransmission are involved in autistic disorders (Shinohe et al. 2006; Smith et al. 2011). Indeed, NMDA antagonists have become the focus of increasing interest in the treatment of obsessive–compulsive disorder, schizophrenia and mood disorders (Zdanys & Tampi, 2008). In agreement with the hypothesis of this study, the results of this trial based on analysis of multiple subscales of ABC-C show that treatment with memantine as adjuvant to risperidone for 10 wk results in significantly greater reduction in ABC-C subscale scores for irritability, hyperactivity and stereotypic behaviour compared to placebo. These findings suggest that memantine can be an effective treatment for behavioural problems in children with autism. Clinical characteristics of the patients, such as gender, age and illness duration, did not differ between groups and cannot explain differences in the therapeutic outcome. To the best of our knowledge, there is no report regarding pharmacokinetic interaction between risperidone and memantine. We started both drugs (memantine and risperidone) simultaneously to prevent any loss to follow-up due to long duration of the study. However, this did not affect our results as memantine was superior to placebo in improving

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<th>Table 2. Mean ± S.D. of the two treatment arms on the five subscales of Aberrant Behavior Checklist–Community rating scale</th>
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irritability, hyperactivity and stereotypic behaviour symptoms of autism.

Owley et al. (2006) enrolled 14 subjects aged 3–12 yr in an 8-wk study of memantine for PDD (Owley et al. 2006). Patients received up to 20 mg/d memantine. In addition to cognitive assessments, the ABC-C version for behavioural outcomes was also used. Of these measures, patients showed significant improvement only in memory and behaviour change, including improvements in irritability, lethargy, stereotypy, hyperactivity and inappropriate speech (Owley et al. 2006). Results of this study with regard to irritability, hyperactivity and stereotype behaviours are in line with Owley et al. Nevertheless, their study was an open-label trial.

A retrospective study by Erickson et al. (2007) analysed the use of memantine in 18 patients aged 6–19 yr with PDD. The maximum dose of memantine was 20 mg/d. Outcome measures included the Clinical Global Impression–Severity and Clinical Global Impression–Improvement (CGI-I) subscales and Aberrant Behavior Checklist data. Subjects for whom Aberrant Behavior Checklist data were available showed significant improvement in hyperactivity relative to baseline (Erickson et al. 2007), which is in line with the results of the present study. However, it should be noted that their study was retrospective and small. Chez et al. (2007) conducted an open-label study of 151 patients with autism or PDD–Not Otherwise Specified with an age range of 2.58–26.33 yr. Patients received a maximum dosage of 30 mg/d memantine. Clinical improvement was demonstrated in 70% of patients, with significant improvement demonstrated in language, behaviour and self-stimulatory stereotypic behaviour, as rated by the CGI-I (Chez et al. 2007). Nevertheless, objective assessments were not used in this study. Chez et al. (2007) observed worse irritability, hyperactivity and manic-type behaviours in 18/150 (11.84%) of patients, whereas the present study reports improvements in the irritability subscale. In addition, unlike the results of the present study, they reported improvements in receptive language and social behaviour. Niederhofer (2007) described a case series study investigating the effect of memantine in the treatment of autism. Four patients were enrolled: two with Asperger type; one with Kanner type; one with atypical autism. Subjects received memantine at doses of 20 mg/d for 4 wk and outcomes were measured by the Aberrant Behavior Checklist. Significant improvement was noted for irritability, hyperactivity and inappropriate speech (Niederhofer, 2007).

To our knowledge, this study represents the first double-blind, placebo-controlled study of memantine in children with autism. However, the present study is in line with previous reports regarding the role of NMDA antagonist in the treatment of autism (Erickson et al. 2007; Niederhofer, 2007; Owley et al. 2006). In the present study, the period of follow-up was relatively short and requires that the results be confirmed in longer, randomized, controlled trials. There was no significant difference in the frequency of side-effects and extra-pyramidal effects. Nevertheless, it may be possible that the study was relatively small to determine differences in side-effect rates and this should be considered as a limitation of the present study. In conclusion, the present study indicates memantine as a potentially well-tolerated adjunctive treatment strategy for autism. Nevertheless, monotherapy studies with memantine are warranted to further assess its efficacy in the treatment of autism.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145712000880

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Statement of Interest

None.

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