with lead. Lead-induced attenuation of jumping also was potentiated in the presence of L-NAME, while diarrhea was decreased by the low dose of the drug. These data also s how that nitric oxide may involve in development of dependency and lead-induced attenuation of jumping.

Acknowledgement

The authors wish to thank Dr. T. Nayer-Nouri for his assistance in preparing this manuscript.

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5-Ht3 Antagonist for Cognition Improvement in Schizophrenia: A Double Blind, Placebo-Controlled Trial

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Article info:
Received:15 September 2009
First Revision: 15 Octoer 2009
Accepted: 10 November 2009

Key Words:
Cognitive Impairments,
5-HT3,
Schizophrenia

A B S T R A C T

Introduction: Patients with schizophrenia characteristically exhibit cognitive deficits. The level of cognitive impairment is found to predict the functional outcome of the illness more strongly than the severity of positive or negative symptoms. The purpose of this study was to assess the efficacy of ondansetron, a 5-HT3 receptor antagonist as an adjuvant agent in the treatment of chronic schizophrenia in particular for cognitive impairments.

Methods: This investigation was a 12-week, double blind study of parallel groups of patients with stable chronic schizophrenia. Thirty patients were recruited from inpatient and outpatient departments. All participants met Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia. To be eligible, patients were required to have been treated with a stable dose of risperidone as their primary antipsychotic treatment for a minimum period of 8 weeks. The subjects were randomized to receive ondansetron (8 mg/day) or the placebo in addition to risperidone. Cognition was measured by a cognitive battery. Patients were assessed at baseline and after 8, and 12 weeks after the medication started.

Results: Administration of ondansetron significantly improved visual memory based on improvement on visual reproduction, visual paired associate and figural memory sub tests of Wechsler Memory Scale Revised.

Discussion: The present study indicates ondansetron as potential adjunctive treatment strategy for chronic schizophrenia particularly for cognitive impairments.

1. Introduction

Schizophrenia is a devastating neurobiologic disorder that typically strikes the brain function of adolescents and young adults, occulting in about 1 of every 100 people worldwide (1). The direct costs of schizophrenia accounted for 2.5% of US health expenditures. Despite these expenditures, up to half of all people with schizophrenia at any point in time are not receiving active psychiatric care, and at least 15% to 20% of people suffering from the disorder will never receive any psychiatric treatment (2). Moreover, although the financial costs of schizophrenia can be calculated, the cost of unrealized human potential and lost dignity associated with the disease are beyond computation. For all of these reasons, advances in the treatment of schizophrenia have been and continue to be urgently needed (3-4).

Patients with schizophrenia characteristically exhibit cognitive deficits. The level of cognitive impairment is

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found to predict the functional outcome of the illness more strongly than the severity of positive or negative symptoms (3-4). Cognitive impairment is estimated to occur in 75%-85% of patients with schizophrenia and often precedes the onset of other symptoms. The treatment of cognitive impairments may be essential for improving the quality of life of patients with schizophrenia (4-5). The main cognitive domains affected include verbal and working memory, executive functioning, sustained attention, visual-spatial performance, and processing speed (4-5). Despite appropriate treatment with either typical antipsychotics or atypical antipsychotics, patients with schizophrenia continue to exhibit cognitive impairments. The lack of marked cognitive benefit of antipsychotics has led to the investigation of alternative agents or polypharmacy for the treatment of cognitive deficit (6-10). 5-HT3 (5-hydroxytryptamine3) receptors are prime candidates due to their functional diversity to treat cognition impairments in patients with schizophrenia (11-12). 5-HT3 receptor antagonists have been reported to be a novel agent for cognition improvement in patients with schizophrenia (12). Among the receptors for serotonin, the 5-HT3 receptor is the only ligand-gated ion Channel (11-13). In pre-clinical studies, the injection or infusion of dopamine, amphetamine or 2-methyl-5-HT into limbic brain areas enhanced locomotor behavior in the rat and this was blocked by ondansetron a 5-HT3 receptor antagonist (12). It has also been shown that ondansetron, at a low dose of 0.01mg/kg, blocked the amphetamine induced disruption of latent inhibition in the rat. Ondansetron was found to have dose-related beneficial effects on learning and memory (12). Several case reports and open-label, small-scale trials have found that ondansetron is an effective add-on therapy in controlling psychotic symptoms and adverse motor effects associated with neuroleptics, although its effectiveness for cognitive impairment remains inconclusive (14-17). A recent study showed that short-term administration of ondansetron, was associated with significantly improved visuo-spatial memory as measured by the Rey–Osterich Complex Figure test in patients with schizophrenia (17). In addition, another study presented that ondansetron enhances the effectiveness of haloperidol for chronic, treatment-resistant schizophrenia, particularly for negative and cognitive symptoms (18). To the best of our knowledge, the study of Levkovitz et al (17) is the only published study that has used a cognitive battery consisting major domains of cognition (including attention, working memory, executive function, verbal memory, visual memory and construction), to assess the efficacy of ondansetron for cognition improvement in schizophrenia. These studies suggest the need for further rigorous, double blind and placebo controlled trial, to evaluate the therapeutic effect of ondansetron on different domains of cognition schizophrenia.

2. Methods

2.1. Setting

This investigation was a 12-week, double blind study of parallel groups of patients with chronic schizophrenia and was undertaken in Roozbeh Psychiatric Hospital (Tehran, Iran) and Dr. Beheshti Hospital (Zanjan, Iran) from January 2006 to January 2008.

2.2. Patients

Thirty patients were recruited from both inpatient and outpatient departments, although most patients were outpatients (28), and some had brief periods of hospitalization during the study (11 women and 19 men), age ranging from 22 to 44 years. All participants met DSM-IV-TR (American Psychiatric Association, 2000)(19) diagnostic criteria for schizophrenia. A structured diagnostic procedure, including chart reviews, preceded a census diagnosis with a senior clinician. To be eligible, patients were required to have been treated with a stable dose of risperidone as their primary antipsychotic treatment for a minimum period of 8 weeks before entry into the study. In addition, subjects needed to demonstrate a minimum period of 4 weeks symptom stability, defined as no more than 20% change on consecutive ratings on the Positive and Negative Syndrome Scale (PANSS) (20).

The level of cognitive impairment required for participation was defined as a total performance score at least 20 on Mini-Mental State Examination (21). The 17-item Hamilton's Rating Scale for Depression was administered mainly to assess the presence of depression which could affect cognitive performance (22). Patients were excluded if they had any medical diagnoses (including ECG conduction abnormalities, neurological disorder, or an active seizure) or were receiving medications that may have affected cognitive performance. Subjects who met the criteria for a DSM IV diagnosis of alcohol or substance abuse (other than for nicotine) within the last month or the criteria for DSM-IV alcohol or substance dependence (other than for nicotine) within the last 6 months were excluded. Furthermore, the following psychotropic medications were not allowed for the duration of the study: anticholinergics, sedating antihistaminics, antidepressants, mood stabilizers, or a second antipsychotic (as adjuvant therapy). Pregnant or lactating women and those of reproductive age without adequate contraception were also excluded.

The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant Number: 2727). The patients provided informed consent in accordance with the procedures outlined by the local IRB, and were informed that they could withdraw from the experiment at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (World Medical Association, 2000) (23).

2.3. Intervention

After baseline evaluation of the severity of psychotic symptoms and cognitive impairments, 30 subjects entered a 12-week, double blind, parallel trial of ondansetron adjunctive treatment.

The subjects were randomized in a 1:1 pattern to receive ondansetron (8 mg/day) or the placebo in addition to risperidone (4-6 mg/day). Ondansetron and placebo were prepared in identical appearance, which were dispensed every 4 weeks; surplus tablets were counted each study visit. Cognition was measured by a cognitive battery. To decrease the practice effect of our cognitive battery, we assessed the patients only twice over the trial for cognitive tasks. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry. A cognitive battery measuring 6 major domains (attention, working memory, executive function, verbal memory, visual memory and construction) was utilized. The Wisconsin Card Sorting Test (24) was used to assess executive functions of changing categories. From the Wechsler Memory Scale-Revised (25), three subtests including figural memory, visual reproduction and visual paired associates were administered to assess visual memory, and two subtests including logical memory and verbal paired associates were administered to assess verbal memory. Although all of the tests utilized assess attention to a certain degree, the digit-span subtest from the WMS-R was particularly administered to evaluate attention and working memory. The Wechsler Adult Intelligence Scale (WAIS-R; 23) block design subtest was used to evaluate construction ability. All patients went through a physical examination before entering the study. As safety measurements, laboratory evaluations, consisting of complete blood count and creatinine, GGT (Gamma-Glutamyl Transferase), ALT (Alanine Amino Transferase), AST (Aspartate Amino Transferase), total bilirubin and fasting serum glucose levels, were performed for each patient at baseline, 8 week and at the end of the study (at 12 week). The findings were within the normal range. Cognitive performance was used as the main outcome measures.

2.4. Statistical Analysis

The cognitive variables were analyzed using Student's t test of difference scores between baseline-ondansetron and baseline-placebo and endpoint-ondansetron and endpoint-placebo. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was performed. All tests were two-tailed with level of significance set at 0.05. Results are presented as mean ± SD. Data were analyzed using commercially available statistical packages (SPSS 13.00. Chicago, IL, USA).

3. Results

Eighty six patients were screened for the study and 30 were randomized to trial medication (15 patients in each group) (Fig. 1). No significant differences were identified between patients randomly assigned to the group 1 or 2 condition with regard to basic demographic data including age, gender, marital status, level of education, mean duration of illness and number of life-time hospitalization (Table 1). All 30 patients completed the trial.

3.1. Neurocognitive Assessments

Table 2 provides the results of cognitive tests for both groups at week 0 and week 12. No statistically significant differences were observed between the two groups at week 0 for any of the cognitive measures. There were no differences between the ondansetron and placebo groups on any cognitive deficits at endpoint except for visual reproduction 1, visual reproduction 2, visual paired associate 1, visual paired associate 2 and figural memory.

3.2. Hamilton's Rating Scale for Depression

There were no differences between the ondansetron and placebo groups on Hamilton's Rating Scale for Depression at week 0 (8.20 ± 1.52 and 7.33 ± 1.62 for ondansetron and placebo respectively; mean ± SD; P = 0.42) and week 12 (7.80 ± 0.94 and 7.46 ± 1.55 for ondansetron and placebo respectively; mean ± SD; P = 0.48)

3.3. Clinical Complications and Side Effects

Seven side effects including constipation, insomnia, dizziness, muscle cramp, diarrhea, dry mouth and vomiting were observed over the trial. The difference between the ondansetron and placebo in the frequency of side effects was not significant.

Table 1. Baseline data

	Ondansetron Group	Placebo Group	P
Gender	Male: 10, Female: 5	Male: 9, Female: 6	1.00
Age (Mean±SD)	33.00 ± 5.88 (year)	33.53 ± 5.95 (year)	0.48
Marital Status	Single: 9, Married: 4, Divorced: 1	Single: 10, Married: 3, Divorced: 2	1.00
Level of Education	Under diploma:8, Diploma: 6, Higher Diploma: 1	Under diploma:9, Diploma: 4, Higher Diploma: 2	1.00
Time Since Diagnosis	7.10 ± 3.43 (year)	7.32 ± 3.98 (year)	0.87
Number of Life-Time Hospitalization (Mean±SD)	4.26 ± 1.83	4.46 ± 1.68	0.75

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Table 2. The neuro cognitive assessments

	Ondansetron Week 0 (n=15) Mean ± SD	Placebo Week 0 (n=15) Mean ± SD	P	Ondansetron Week 12 (n=15) Mean ± SD	Placebo Week 0 (n=15) Mean ± SD	P
WCST-Categories completed	2.15 ± 0.60	2.08 ± 0.68	0.75	2.40 ± 0.45	2.24 ± 0.45	0.34
WCST-Categories error	37.86 ± 14.02	36.66 ± 18.41	0.84	34.40 ± 11.74	33.33 ± 16.95	0.84
Figural Memory	5.46 ± 1.21	5.20 ± 1.17	0.54	6.76 ± 0.72	5.33 ± 1.08	0.0002
Visual Paired Associates 1	8.60 ± 3.52	8.80 ± 3.76	0.88	10.43 ± 2.65	8.26 ± 3.06	0.04
Visual Paired Associates 2	3.60 ± 1.54	3.96 ± 1.56	0.53	4.90 ± 0.89	4.00 ± 1.37	0.04
Visual Reproduction 1	32.06 ± 2.86	31.80 ± 4.26	0.84	35.36 ± 5.44	31.86 ± 4.12	0.05
Visual Reproduction 2	28.66 ± 4.37	28.40 ± 4.46	0.86	32.26 ± 3.59	29.60 ± 3.62	0.05
Logical Memory 1	19.73 ± 2.43	20.06 ± 4.66	0.80	22.80 ± 2.39	22.46 ± 4.58	0.80
Logical Memory 2	19.26 ± 3.51	19.93 ± 3.63	0.61	21.20 ± 2.27	20.93 ± 3.26	0.79
Verbal Paired Associates 1	16.73 ± 2.54	16.46 ± 2.35	0.76	17.93 ± 2.18	17.20 ± 1.89	0.33
Verbal Paired Associates 2	6.43 ± 1.11	6.63 ± 1.87	0.72	7.03 ± 1.17	6.96 ± 1.82	0.90
Digit Span Forward	5.66 ± 1.04	6.10 ± 1.33	0.33	6.23 ± 0.96	6.30 ± 1.29	0.87
Digit Span Backward	5.06 ± 0.92	5.23 ± 0.92	0.62	5.63 ± 1.02	5.70 ±0.92	0.85
Block Design	26.93 ± 5.27	27.66 ± 4.48	0.68	29.53 ± 5.31	29.00 ± 3.44	0.74

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4. Discussion

Studies to improve the cognition impairments of community-based patients with schizophrenia are particularly important to facilitate their continued remission. It has been reported that central 5-HT3 receptors are involved in the pathogenesis of psychotic disorders and cognition impairments (12). Antagonism of the 5-HT3 receptor is thought to have therapeutic effect in treatment of patients with schizophrenia (17-18). Administration of ondansetron significantly improved visual memory based on improvement on visual reproduction, visual paired associate and figural memory sub tests of WMS-R (12).

Clinical characteristics of the schizophrenic patients, such as sex, age and duration of illness, did not differ between groups and can not explain differences in the therapeutic outcome. Moreover, there were no differences between the ondansetron and placebo groups on Hamilton's Rating Scale for Depression over the period of trial. Indeed, the scores of Hamilton's Rating for Depression were stable over the period of study and the observed mild depression symptoms could not affect the cognitive performance. Therapeutic benefit of adjunctive ondansetron in schizophrenia is probably due to its 5-HT3 receptors antagonism. In addition, therapy with 8 mg/day of ondansetron was well tolerated, and no clinically important side effects were observed. Constipation was most common event during the trial with ondansetron.

Like other antipsychotic drugs, risperidone antagonizes 5-HT3 receptors (1). It is reasonable to assume however that ondansetron can have a differential enhancement on memory, when given to risperidone-treated patients. Risperidone and ondansetron might be involved in different mechanisms by which memory function is improved. It has been reported that the beneficial effect of ondansetron on memory and learning is due to its presynaptic depletion of serotonin while risperidone enhances memory function by antagonizing post-synaptic 5-HT3 receptors (17). A plausible explanation might be the low binding affinity of risperidone to 5-HT3 receptors (1). In addition, receptor binding studies have shown a considerable density of the 5-HT3 receptors in the human prefrontal cortex, nucleus accumbens, hippocampal formation, and amygdale: brain regions known to be involved in the pathogenesis of emotional, motivational, and cognitive disorders (12). These studies may suggest a possible explanation for the positive effects of adjunctive ondansetron observed in the present study, i.e., better improvement for negative and cognitive symptoms, and reduced adverse side effects associated with risperidone.

In line with other studies, ondansetron in the present trial enhanced visual memory in patients with schizophrenia (17). Nevertheless, it did not improve other domains of cognition in this group of patients. As the design of the present clinical trial was double blind we tried to decrease the risk of practice effect for the WAIS-R and WCST.

Generally speaking, the present study indicates ondansetron as a potential adjunctive treatment strategy for cognitive impairments.

Acknowledgement

This study was Dr. Neyousha Mohammadi's postgraduate thesis. This study was supported by a grant from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh (Grant No: 2727).

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