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A comparison of the effects of reboxetine and placebo on reaction time in adults with Attention Deficit-Hyperactivity Disorder (ADHD)

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ABSTRACT

Objective: Some studies have demonstrated that Reaction Time (RT) is longer in patients with ADHD which in turn may be associated with educational and occupational impairment and increased driving risks. Any alteration on RT which is induced by the treatment in this population may have great consequences positively or negatively. This study was designed to examine the effects of reboxetine on RT in adults with Attention Deficit-Hyperactivity Disorder (ADHD).

Methods: A total of 30 adult patients with ADHD who did not suffer from any other major psychiatric disorder were eligible to participate in this double blind, placebo controlled study. Patients were randomly assigned to receive either reboxetine (4 mg/day for one week, then 8 mg/day) or placebo for 4 weeks. RT was assessed at baseline and after 4 weeks by validated software which collects and analyses the data for auditory and visual stimulants. Numbers of correct responses, omission and substitution errors for each stimulus were calculated.

Results: Regarding visual tasks and in comparison with baseline scores, the number of correct responses increased significantly and the number of omission errors decreased significantly after 4 weeks of treatment ($P<0.05$) in both groups. However, with regard to auditory tasks scores, no significant differences were found at the end of the study compared to the baseline in each of the two groups. Additionally, no significant differences were noted between the two groups when both visual and auditory tasks were considered.

Conclusion: Results of this study showed that reboxetine did not affect the RT of the patients when both visual and auditory tasks were assessed. Further studies with larger number of patients and for a longer period of time are required to confirm the result of this study.

Keywords: Visual and auditory tasks, Omission and Substitution errors.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common psychiatric disorder that occurs in 3-7% of school aged children (1-4). Many of these children do not receive any treatment and ADHD often persists into adulthood (2, 5). The primary symptoms of ADHD involve different degrees of inattention, hyperactivity, impulsivity and distractibility (2, 5, 6). Some symptoms of ADHD such as hyperactivity usually decrease with increasing age and maturation, however impulsivity and inattention often remain unchanged (5).

Some studies have shown that children with ADHD tend to have longer Stop Signal Reaction Time (SSRT) in comparison with the healthy population (6-9). Also, results of another study have noted that adults with a history of ADHD in childhood have longer Reaction Time (RT) (10). Longer RT is associated with educational and occupational impairment and increases driving risks with fatal consequences (5, 11). A study which was conducted in the UK with a sample size consistsed of 6424 participants and 21 years follow up, demonstrated that longer reaction times and poorer cognitive performance are related to an increased risk of mortality (12). Reaction time is also important in sport fields (13).

Pathophysiology of ADHD has been related to dysfunction of catecholaminergic neurotransmitters system (1-3). As a result, stimulants and noradrenaline reuptake inhibitors have been considered as cornerstone of ADHD treatment (1). Some studies support using methylphenidate (a stimulant) as a treatment for ADHD in most adults (9, 14). Due to some side effects of stimulants

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including changes in appetite and insomnia and due to their potential for abuse, the use of non-stimulant drugs may be preferred.

Atomoxetine is a selective inhibitor of noradrenaline transporter that has a minimal affinity for the serotonin and dopamine transporters (2, 15, 16). It is the first medication approved for the treatment of ADHD in adults. It has a safe and efficient profile (1) but is rather expensive (17). Reboxetine which was first marketed as an antidepressant (18), is a selective norepinephrine reuptake inhibitor and has a similar transporter/receptor profile as atomoxetine (1) and has been recently studied in the treatment of ADHD (19-21).

It has been reported that RT is longer in ADHD patients (10) and the use of some other drugs including CNS-suppressants is also associated with increased RT which may lead to unwanted consequences like occupational and driving accidents in these patients (22, 23). This double blind, randomized, placebo-controlled trial was designed to examine the effect of reboxetine on RT in adults with ADHD. Positive, negative or lacks of effect of the drug on RT in the study patients were matters of concern in this study.

Patients and methods

Thirty adults 18 years old or older participated in this study. Since prevalence of ADHD in parents of children with ADHD is relatively high (2), the subjects were selected among parents of children and adolescents with ADHD who had referred to adolescent psychiatry clinics of Imam Hossein and Roozbeh hospitals affiliated with Shaheed Beheshti University of Medical Sciences and Tehran University of Medical Sciences respectively. The diagnosis of ADHD was established by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV–TR) criteria (24). The information about ADHD history in childhood was confirmed by one of the family member of each patient who remembered patient's manners and behaviors in childhood. In addition, each subject completed a self reported Conner's global index questionnaire; those who obtained the minimum score entered the study.

Demographic information and results of Hamilton anxiety and depression questionnaires were collected for each person at the beginning of the study. None of patients were taking psychotropic medications for at least 2 weeks before the initiation of the study. Exclusion criteria included presence of any other psychiatric disorders such as bipolar mood disorder and major depressive disorder, mental retardation, major medical illness such as hyperthyroidism, cardiovascular, kidney or pulmonary disease, pregnancy or lactation, drug or alcohol abuse and a history of seizure disorder. Patients who forgot taking at least 4 doses of their medications during the whole period of the study or missed at least 3 sequential doses as well as those with blood pressure above 140/90 mmHg were also excluded from the study. After verbal explanation of the study, each participant signed an informed consent.

Patients were randomly divided into two groups. One group received reboxetine and the other received placebo. All subjects received reboxetine or placebo for 4 weeks. Reboxetine was started at a dose of 4 mg once a day in the morning and after one week the drug dose was increased to 4 mg twice a day, one in the morning and one in the evening.

All participants were tested using software installed on a PC which was designed and validated by the authors under supervision of Islamic Azad University, Pharmaceutical Sciences Branch (IAUPS)-information technology division. It consisted of two tasks measuring RT to visual and auditory stimulants. Test procedures were presented either on a computer screen or speakers. Instructions were given orally and they were allowed to practice each test once to become familiar with the task. Visual task was included a series of colors (green, red, yellow and blue) presented in the computer screen for 1 second. The participants were asked to press the right button related to the color as quickly as possible after it appeared on the screen. In each test, RT for correct responses, number of correct responses, omission errors (lack of responses to target stimuli) and/or substitution errors (the number of incorrect response instead of the correct one) were calculated by the software.

With regard to the auditory task, the participants were asked to press the right button related to the played sound as quickly as it was heard. RTs for correct responses, number of correct responses, omission errors, and/or substitution errors were calculated again by the software.

A total of 30 visual and 30 auditory targets were presented. Each participant performed the test at the beginning and at the end of the study. The same test was performed in both test sections for each patient. Statistical analyses were done by utilizing SPSS version 13 for windows; an alpha level less than of 0.05 was considered as significance of statistical association between variables. Paired sample t test was used to evaluate the effect of reboxetine and placebo on RT at each group at the beginning and end of the study. For comparison between the two groups, independent sample t test was used.

RESULTS

Eleven women and 7 men participated in the reboxetine group, in the control group there were 7 women and 5 men.

The means age of the patients in reboxetine and placebo groups were 31.3 and 32.1 years, respectively and the difference was not significant.

The number of correct responses, omission and substitution errors in response to visual and auditory

Table 1. Correct responses, omission and substitution errors at the baseline and at the end of the study.

Group of the study	Reboxetine (n=18)			Placebo (n=12)		
	Baseline	**End point**	**Pvalue**	**Baseline**	**End point**	**Pvalue**
Visual tasks						
Correct responses	7.5 ± 5.24	12.61± 6.73	<0.001*	11.08± 8.28	16.17 ± 9.57	<0.001*
Substitution errors	8.72 ± 2.76	9.00± 3.31	0.77	8.33± 4.14	6.17 ± 4.34	0.126
Omission errors	13.78 ± 4.85	8.39± 4.02	<0.001*	10.58± 7.14	7.67 ± 6.44	<0.001*
Auditory tasks						
Correct responses	4.72 ± 3.48	6.83 ± 3.99	0.052	7.75 ± 4.99	8.08 ± 1.78	0.259
Substitution errors	12.06 ± 4.17	12.11 ± 4.85	0.968	12.5 ± 5.50	13.75 ± 3.17	0.575
Omission errors	13.22 ± 5.14	11.11 ± 5.48	0.172	9.75 ± 6.21	8.17 ± 4.00	0.196

* : Significant differences at the end of the study in comparison with the baseline in each group (P<0.001)

Table 2. Mean of reaction time (RT) in the reboxetine and placebo groups at the baseline and at the end of the study†.

Group of the study	Reboxetine (n=18)			Placebo (n=12)		
	Baseline	**End point**	**P value**	**Baseline**	**End point**	**P value**
Visual tasks	0.617 ± 0.159	0.646 ± 0.075	0.426	0.596 ± 0.083	0.632 ± 0.105	0.199
Auditory tasks	0.583 ± 0.201	0.573 ± 0.178	0.827	0.668 ± 0.124	0.610 ± 0.105	0.586

† : The data are in mean ± standard deviation (in seconds).

stimuli in both groups at the baseline and the end of the study are presented in table 1.

In visual tasks the number of correct responses increased significantly and the number of omission errors decreased significantly (P<0.05) at the end of the study in comparison with the baseline in both groups. In auditory tasks there were no significant (NS) differences in both groups; independent sample t test showed NS differences between two groups in both visual and auditory tasks. However it was noted that there was a trend toward more substitution errors in the reboxetine group in comparison with the placebo group.(p=0.07)

DISCUSSION

Different therapeutic class of drugs such as stimulants, [e.g. methylphenidate (MPH)], Tricycle antidepressants (TCAs) and several non-stimulant drugs such as atomoxetine and reboxetine are being used to treat ADHD and have been shown to be effective in reducing the symptoms of ADHD (1, 3, 25-28). Several studies have shown that methylphenidate and other stimulants improved SSRT in adults and children with ADHD (6, 27-30), but they have some adverse effects such as decreased appetite, insomnia and potential for abuse (2, 31).

TCAs such as desipramine, amitriptyline and imipramine that have been used for the treatment of ADHD, may increase RT (22, 23). As a result, these drugs are associated with an increase risk of car accidents with fatal consequences (23). A comparison of the effect of reboxetine and amitriptyline on cognitive function and psychomotor performance in healthy subjects, showed that reboxetine had little or no effect on the performance, however amitriptyline increased RT (32). Similarly, the driving risks increased in subjects while taking TCAs (23). Similar results have been reported in patients with major depressive disorder (22).

Atomoxetine is a selective norepinephrine reuptake inhibitor with almost no abuse potential and some studies have shown that it can decrease SSRT in adults with ADHD (33).

Theoretically, reboxetine may decrease RT similar to atomoxetine. At the end of present study, significant differences were observed in the number of correct responses and omission errors in comparison with the baseline values in both reboxetine and placebo groups. These findings were similar to those in previous studies (1, 35). Ferguson et al, compared the effects of reboxetine, paroxetine and placebo in depressed patients and found that reboxetine improved cognitive functions in comparison with the baseline (36).

Results of present study showed that there were no differences in the mean of RT of correct answers compared to the baseline values in both groups. Hindmarch examined the effect of reboxetine and amitriptyline on psychomotor or cognitive function in healthy males. Consistent with the results of this study, it was reported that reboxetine had little effect on psychomotor or cognitive function. On the other hand, amitriptyline, even at low doses, impaired CNS function (37). Siepman et al compared the effects of

reboxetine on cognitive and autonomic functions with those of placebo in healthy subjects and found that reboxetine did not affect choice reaction, memory and psychomotor coordination (38).

Similar to the results of previous studies, the present trial showed that reboxetine did not have any effects on RT (23, 32, 38). It is suggested that reboxetine may be used in the treatment of patients with ADHD without considering negative or positive effects on RT.

In this study, neither reboxetine nor placebo showed any significant effects on the RT. This study was a preliminary study with only 4 weeks duration and with a limited number of patients. Further studies with more patients and longer period of time are required to confirm the result of this study.

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