Original Paper

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Insignificant Effects of Atomoxetine on Thyroid Functions in Children and Adolescents with Attention Deficit and Hyperactivity Disorder in Short Term

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ABSTRACT:

Insignificant effects of atomoxetine on thyroid functions in children and adolescents with attention deficit and hyperactivity disorder in short term

Objective: In this study, we aimed to explore the effects of atomoxetine on thyroid functions in children and adolescents with attention deficit hyperactivity disorder.

Methods: A retrospective chart review was done to evaluate the thyroid function tests of patients diagnosed with attention deficit hyperactivity disorder and treated with only atomoxetine. The thyroid function tests of 38 subjects, from both before atomoxetine was started and during an effective dose of atomoxetine treatment, were found from the patient charts and compared statistically.

Results: There were no statistically significant differences between the baselines levels of thyroid-stimulating hormone (TSH), free T4, and free T3 values and those during an effective dose of atomoxetine treatment. In one subject, four weeks after atomoxetine was started and titrated to the effective dose, an insignificant increase in TSH was observed, which decreased to the normal range after the discontinuation of the atomoxetine treatment.

Conclusion: Therapeutic doses of atomoxetine do not seem to change thyroid functions in children and adolescents with attention deficit hyperactivity disorder.

Keywords: atomoxetine, thyroid functions, attention deficit hyperactivity disorder, adverse effects, children

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common mental disorders, with a worldwide prevalence of around 5% in children[1]. Stimulants and atomoxetine are the first choice of drugs in the treatment of ADHD[2-4]. Atomoxetine, which selectively blocks reuptake at the noradrenergic neuron, is a non-stimulant medication for the treatment of ADHD[5]. It was first approved by the Food and Drug Administration (FDA) in 2002 and is generally well tolerated by children[6-7]. Although atomoxetine is generally safe for the treatment of ADHD, adverse reactions have been reported. The most common adverse reactions include nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence[8]. The most alarming adverse effects are suicidal thoughts and the effects on liver functions and the cardiovascular system[9].

It is mentioned in the literature that psychotropic drugs may affect the hypothalamic pituitary axis (HPA)[10], and in one study it was shown that atomoxetine may affect bedtime cortisol levels[11]. In addition, some drugs (e.g., desipramine) with noradrenergic dominance, like atomoxetine, were shown to possibly affect TSH levels[12]. We hypothesized that atomoxetine would also affect thyroid functions by noradrenergic dominance. In a study with adults using atomoxetine, an increase in thyroid function tests was observed in a single case report[13]. To our knowledge, there was no clinical trials that explored the effects of atomoxetine on thyroid functions in children. In this present study, we aimed to explore the effects of atomoxetine on thyroid functions in children and adolescents with ADHD.

METHODS

Forty-one subjects, who were the participants of another study that investigated the effects of atomoxetine on cardiac rhythm, were included in this retrospective chart review study. Participants were the consecutive patients who were diagnosed with ADHD and started on atomoxetine in the child and adolescent psychiatry outpatient clinic of the Bakirkoy State and Research Hospital for Mental Health and Neurologic Disorders. The study was approved by the Medical Ethics Committee of the Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center and Research Hospital. The parents of the children signed informed consent forms for the cardiac study and allowed us to use any data for medical purposes.

The ADHD diagnosis and comorbid diagnoses were made by clinical assessments according to DSM-IV-TR by experienced child and adolescent psychiatrists. Diagnoses were based on comprehensive information from clinical examination, which included interviews with the parents and children and a review of previous psychiatric and educational records. In addition, DSM-IV criteria checklists for ADHD were used. Participants excluded from this study include those with a chronic medical or neurologic disease, those who were using another drug concurrently with atomoxetine, and those who were unwilling to participate in the cardiac study. We excluded three participants' charts due to missing data. Therefore, 38 participants' charts were eligible for this present study. The thyroid function tests of these 38 subjects, from both before atometine was started and during an effective dose of atomoxetine treatment (approximately at the fourth week of atomoxetine treatment), were found from the files and compared statistically. Blood samples were drawn between 8 to 12 hours after an overnight fasting. TSH, fT3, and fT4 levels were evaluated using the Abbott Architect 2000 device (Abbott Diagnostics, Chicago, USA) and the chemiluminescent microparticle immunoassay method. Thyroid functions were evaluated based on the age appropriate standard reference intervals proposed for the chemiluminescent microparticle immunoassay system which was used in our research (for 6-11 years; TSH: 0.6 – 4.84 ulU/mL, fT4: 0.97 – 1.67 ng/dl , fT3: 2.53 – 5.22 pg/ml and for 11-18 years: TSH: 0.51 – 4.30 ulU/mL, fT4: 0.98 – 1.63 ng/dl, fT3: 2.56 – 5.01 pg/ml).

Statistical Analysis

Statistical analyses were performed using the SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL). A Wilcoxon test was used for repeated consecutive measurements. Statistical significance was set to $p<0.05$.

RESULTS

In total, 38 participants were included in the study. Half of the participants were boys (n=19), the other half were girls (n=19). Mean age, mean height, and mean weight were 9.8±2.5 years (range 6 – 16), 137.5±12.7 centimeters (cm) (range 121 – 170), and 32.7±11 kilograms (kg) (range 19 – 64), respectively. There were no significant differences between girls and boys regarding age, height, and weight ($p>0.05$).

Sixty-three percent of subjects had combined type ADHD, 34% had inattention type ADHD, and

Table 1: Demographic and clinical characteristics of study participants (n= 38)

Characteristics		
Age, years, mean (SD)	9.8 (2.5)	
	n	**%**
Gender		
Boys	19	50
Girls	19	50
ADHD		
Combined subtype	24	63
Inattentive subtype	13	34
Hyperactive-impulsive subtype	1	3
Comorbid psychiatric disorders		
Anxiety disorder	9	24
Oppositional defiant disorder	7	18
Learning disorder	4	11
Tic disorder	4	11
Mood disorder (major depressive disorder)	1	3
Elimination disorder	1	3

disorder had a history of both stimulant and risperidone use, and one subject with comorbid anxiety disorder had a history of fluoxetine use before the atomoxetine treatment. The minimum time between the discontinuation of the previous psychotropic drug and the initiation of the atomoxetine treatment was three months. In all of the subjects who had a history of stimulant use, the discontinuation of the stimulant was due to adverse effects such as headaches, abdominal pain, irritability, and crying spells.

The mean thyroid function tests of all of the subjects before atomoxetine was started and at the 4th week of atomoxetine treatment were shown in Table 2. There were no statistically significant

Table 2: Thyroid function tests at baseline and during effective dose atomoxetine treatment (n=38)

Parameters		n	Before treatment	During effective dose treatment	p
TSH (µIU/mL)	6-11 years	26	2.1±1.2	1.9±0.8	0.482
	11-18 years	12	2.1±1.7	2.0±1.3	0.825
	Total	38	2.1±1.3	2.0±1.2	0.544
fT4 (ng/ml)	6-11 years	26	1.2±0.1	1.1±0.1	0.404
	11-18 years	12	1.2±0.1	1.1±0.1	0.809
	Total	38	1.2±0.2	1.2±0.1	0.380
fT3 (pg/ml)	6-11 years	26	3.6±0.4	3.6±0.6	0.951
	11-18 years	12	4.1±0.5	3.8±0.6	0.057
	Total	38	3.8±0.5	3.7±0.6	0.213

TSH: Thyroid-stimulating hormone, fT4: free T4, fT3:Free T3, values were given as mean±SD

3% had hyperactive-impulsive type ADHD. Demographic characteristics of the subjects were shown in Table 1. Nine subjects had comorbid anxiety disorders, seven subjects had comorbid oppositional defiant disorder, four subjects had comorbid learning disorder, four subjects had comorbid tic disorder, one subject had comorbid depression, and one subject had comorbid elimination disorder. The mean initial dose of atomoxetine was 16 mg/day (min: 0.4 mg/kg/day – max: 0.6 mg/kg/day), and the mean maintenance dose was 33 mg/day (min: 1 mg/kg/day – max: 1.2 mg/kg/day). Thirty subjects were diagnosed with ADHD for the first time at the time of referral, and atomoxetine was the first psychotropic drug they used. Six subjects had a history of stimulant use. One subject with comorbid oppositional defiant

differences between the pre-treatment and during-treatment thyroid function tests of the subjects. In one subject, four weeks after atomoxetine was started, an increase in the TSH level was observed, without any associated clinical signs and symptoms. The atomoxetine treatment was stopped with the advice of pediatric endocrinology department, and after atomoxetine was stopped, the TSH level was decreased to normal range. In this subject, it was also observed that the basal TSH level was slightly higher than the normal range.

DISCUSSION

To our knowledge, this study is the first to explore the effects of atomoxetine treatment on thyroid functions in children and adolescents. Except for

one subject, we observed that atomoxetine has no effect on thyroid functions. In the subject who had an increase in TSH level after the atomoxetine treatment, the baseline TSH level (the TSH level before atomoxetine treatment) was also slightly higher than the normal range, so it is not clear if the TSH increase was due to atomoxetine or due to another factor before atomoxetine was started. But also it is possible that atomoxetine may have increased TSH level in an already vulnerable individual. In the literature, abnormal thyroid function tests due to an atomoxetine treatment were reported in only one adult patient. In a study with 20 adult subjects using atomoxetine, an increase in thyroid function was observed in a single case during a follow-up, which decreased to the normal range after stopping atomoxetine[13]. In another study, Adler et al. followed 384 adult patients using atomoxetine for approximately four years, and they reported that they observed no thyroid function abnormalities in laboratory test results done periodically[14].

It is mentioned in the literature that psychotropic drugs may affect the HPA axis with various mechanisms. In one particular study, it was shown that children with ADHD on atomoxetine treatment had higher cortisol levels at bedtime than non-medicated children with ADHD[11]. Thyroid function changes due to psychotropic drugs have been reported in many studies[12]. For example, it is known that lithium, valproic acid, and quetiapine affect thyroid functions[10]. In a study from Turkey, reboxetine, which is a selective noradrenaline reuptake inhibitor like atomoxetine, was reported to change TSH and T4 levels[12]. In this study, Eker et al. examined the effects of different classes of antidepressants on thyroid functions. They showed that, in the group of depressive patients using reboxetine, the TSH level was significantly reduced, while the T4 level was significantly increased, after 11 weeks of treatment. Melander et al. showed that noradrenalin affects the metabolism of thyroid hormones, and both noradrenaline and adrenaline have an influence on thyroid hormone metabolism and increase the deiodination of thyroid hormones[15]. In addition, some studies showed that desipramine and nortriptyline, which have noradrenergic dominance like atomoxetine, might have effects on TSH levels[12]. These tricyclic antidepressants generally exert their therapeutic effects through a modulation of the monoaminergic systems, and the monoaminergic systems influence the HPA in different ways, such as enhancing thyrotropin-releasing hormone (TRH) release, changing the thyroid hormone secretion by adrenergic nerves, or influencing thyroid hormone metabolism and increasing the deiodination of thyroid hormones[15]. Noradrenaline is also known to affect the neuroendocrine systems that modulate growth[16]. Therefore, it is possible that an increased noradrenergic tone due to atomoxetine may have an effect on the HPA axis and change the TSH levels.

Individuals with hyperthyroidism show symptoms like hyperactivity, irritability, mood swings, insomnia, anxiety, perspiration, palpitations, and weight loss[17]. Some studies observe that the adverse effects of atomoxetine, like mood swings, irritability, insomnia, weight loss, and arrhythmia, resemble the symptoms of hyperthyroidism[18,19]. Due to the similarities between the symptoms of hyperthyroidism and the adverse effects of atomoxetine, thyroid hormone level changes may be unrecognized in patients who are using atomoxetine. Clinicians should keep this in mind and pay a particular attention for possible thyroid hormone level changes when patients complain about any of the adverse effects listed above.

Limitations and strengths of the study

The strength of this study is that it is the first clinical study that explored the effect of atomoxetine on thyroid functions in children and adolescents with ADHD. All children and adolescents included in the study had no chronic medical or neurologic disease, and none of the subjects was using any other medications concurrently with atomoxetine. Hence, the factors that may have an effect on thyroid functions were minimized. However, this study has several methodological limitations. First, the sample

was non-randomized, so these results may not be representative of all children and adolescents with ADHD. Second, the limited number of subjects and the retrospective design of the study may have interfered with the results. Third, the maximum daily dose of atomoxetine used in this study was lower than the maximum daily doses suggested in ADHD treatment algorithms[20,21], and in some studies, a 1.8 mg/kg/day dosage was found to be more effective (although not approved by the FDA)[22,23]. Therefore, we wonder if higher daily doses of atomoxetine would have had a different effect on thyroid functions.

CONCLUSIONS

We observed a TSH level increase in one subject during the atomoxetine treatment, but this increase did not give rise to clinical signs and symptoms, and the TSH level decreased to the normal range after stopping atomoxetine. In the short term, therapeutic doses of atomoxetine do not seem to change thyroid functions in children and adolescents with ADHD. Nevertheless, there is a need for randomized, double blind, placebo-controlled studies that further explore the effects of atomoxetine on thyroid functions.

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