Cardiology in the Young (2012), **22**, 158–161
doi:10.1017/S1047951111001211

Original Article

Effects of atomoxetine on cardiovascular functions and on QT dispersion in children with attention deficit hyperactivity disorder

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Abstract *Background:* Atomoxetine is a central norepinephrine reuptake inhibitor used to treat attention deficit/hyperactivity disorder. The effects of atomoxetine on cardiovascular functions and QT dispersion in children with attention deficit/hyperactivity disorder have not been previously reported. The aim of this study was to analyse cardiovascular functions and QT dispersion on the surface electrocardiogram of children with attention deficit/hyperactivity disorder during atomoxetine therapy. *Methods:* A total of 40 children – with a mean age of 8.6 plus or minus 2.3 years and a median age of 11 years; ranged from 8 to 14 years – with attention deficit/hyperactivity disorder – with six girls and 34 boys – were included in the study. We recorded the mean systolic and diastolic blood pressure, heart rate, corrected QT interval, QT dispersion, and left ventricular systolic functions at baseline and 5 weeks after atomoxetine therapy. *Results:* Atomoxetine decreased baseline mean systolic and diastolic blood pressure; baseline mean heart rate decreased; and baseline mean corrected QT interval and QT dispersion mildly increased. Atomoxetine decreased baseline mean ejection fraction and baseline mean shortening fraction. *Conclusion:* The results of our study suggest that atomoxetine does not cause clinically significant alterations in QT dispersion, systolic and diastolic blood pressure, heart rate, corrected QT interval, and left ventricular systolic functions during short-term treatment in children with attention deficit/hyperactivity disorder.

Keywords: Echocardiography; norepinephrine reuptake inhibitor; QT interval

Received: 2 June 2011; Accepted: 17 July 2011; First published online: 25 August 2011

Attention deficit/hyperactivity disorder is characterised by a persistent high level of hyperactive, inattentive, and impulsive behaviour in children and adolescents. Despite the fact that information on the prevalence and incidence of attention deficit/hyperactivity disorder in Europe is scarce, and depending on the definition used, a range of 2–5% – for children aged 6–16 years – has been reported in most of the studies based on the ICD-10 and DSM-IV diagnostic criteria, respectively.[1]

Atomoxetine is a central norepinephrine reuptake inhibitor, which has recently been approved in the United States of America for treatment of patients with attention deficit/hyperactivity disorder.[2,3] Adverse effects on the cardiovascular system, including abnormalities in heart rate, blood pressure, or cardiac rhythm, in children taking atomoxetine have been reported previously.[3]

QT dispersion reflects variations in the repolarisation in different regions of the myocardium. These result from re-entrant mechanisms owing to the existence of areas of slow conduction.[4,5] The measurement of the QT interval dispersion has been studied as an electrocardiogram marker of ventricular repolarisation abnormality, risk of fatal arrhythmias, and therapeutic evaluation of the drugs.[6,7] Despite the widespread clinical use of atomoxetine in children, adolescents, and adults, to date, there are no reports

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with regard to the effects of atomoxetine on QT dispersion in children with attention deficit/hyperactivity disorder. It is noteworthy that most studies in this area have focused on corrected QT interval; however, QT dispersion is an important additional risk indicator for subsequent cardiovascular events, particularly arrhythmias, especially in vulnerable individuals.[8] However, the effects of atomoxetine on left ventricle systolic functions by echocardiography have not been studied. In this study, we prospectively analysed the changes in cardiovascular functions and QT dispersion on the surface electrocardiogram of children with attention deficit/hyperactivity disorder during atomoxetine treatment.

Materials and methods

Study population

This study enrolled all children in the age group of 8–14 years with attention deficit/hyperactivity disorder who were treated with atomoxetine at the Child Psychiatry Department, Konya Training and Research Hospital, over a period of 6 months, from September, 2010 to February, 2011. The local ethics committee approved this study, and written informed consent was obtained from parents of all patients.

Patients met diagnostic criteria for attention deficit/hyperactivity disorder based on the DSM-IV-TR and assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia.[9] Atomoxetine was initiated at a standard specified dose – 0.5 milligram per kilogram per day – in all patients and increased to 0.8–1.2 milligram per kilogram per day according to parents and clinician's report after the first week. Medical history, vital signs – including heart rate, and systolic and diastolic blood pressure – electrocardiograms, and echocardiography were obtained from all patients. Patients who had seizures, bipolar disorder, psychotic illness, mental retardation, pervasive developmental disorder, and who were taking psychotropic medications were excluded from the study. None of the patients had systemic disease or were taking drugs known to influence the heart rhythm and electrocardiogram. None of the patients had electrolyte abnormalities.

Electrocardiogram analysis

We obtained a 12-lead electrocardiogram with a paper speed of 50 millimetres per second and 1 millivolt per centimetre standardisation from all patients (Nihon Kohden electrocardiogram, Cardiofax GEM, Model 9022 K, Tokyo, Japan). Electrocardiogram tracings were blindly analysed in all patients at baseline and 5 weeks after atomoxetine therapy. We calculated the heart rate and QT dispersion in four successive complexes for each lead. The QT interval was measured manually in all 12 leads by the same paediatric cardiologist in order to exclude inter-observer variability. To improve accuracy, measurements were recorded using calipers and magnifying lens. The QT interval was measured starting from the onset of the QRS complex until the end of the T wave, which is the return of the T wave to the baseline. When the U wave was present, the QT interval ended at the midpoint between the T and U waves, which was obtained at the intersection of a line taken tangentially to the repolarisation line with the isoelectric line.[4] Correction of the QT interval was obtained using Bazett's formula.[10] QT dispersion, defined as the difference between maximum and minimum QT, was calculated on the basis of the QT intervals obtained in the 12 leads.

Echocardiographic examination

All patients underwent echocardiographic examination after diagnosis of attention deficit/hyperactivity disorder and before atomoxetine treatment. All echocardiographic examinations were performed with a commercially available echocardiographic machine, specifically a ProSound Alpha 7 (Aloka, Japan), equipped with 3- and 5-megahertz transducers. A standardised cross-sectional and Doppler echocardiographic examination was performed with multiple orthogonal parasternal, apical, and subcostal views with the patient in left lateral decubitus position. The systolic function of the left ventricle was evaluated using M-mode echocardiography in the parasternal long-axis view. Fractional shortening was calculated as defined previously.[11]

Statistical analysis

The results were statistically analysed. The mean values of each variable in the initial and follow-up examination were compared, using a paired t-test. A p-value < 0.05 was considered statistically significant.

Results

There were no clinically adverse effects such as palpitations, presyncope, or syncope during the study period. During the study period, 40 children with attention deficit/hyperactivity disorder were evaluated. There were 6 (15%) girls and 34 (85%) – boys. The mean age of the patients was 8.6 plus or minus 2.3 years, with a median of 11 years and a range of 8–14 years. Table 1 shows the demographic, electrocardiographic, and echocardiographic characteristics of the patients at baseline and 5 weeks after atomoxetine therapy.

Systolic and diastolic blood pressure, and heart rate values after 5 weeks of treatment were found to be lower when compared with the baseline values;

https://doi.org/10.1017/S1047951111001211 Published online by Cambridge University Press

Table 1. Parameters obtained at baseline and 5 weeks after atomoxetine therapy.

	Baseline	After treatment	p-value
Number of patients	40	40	
Sex			
Girl (%)	6 (15)		
Boy (%)	34 (85)		
Weight (kg)	30 (9.5)		
Systolic blood pressure (mmHg)	94.8 (8.5)	93.5 (12.3)	0.486
Diastolic blood pressure (mmHg)	61.2 (10.1)	60.7 (7.3)	0.802
Heart Rate (beats/min)	88.3 (17.5)	85.4 (15.3)	0.097
QTc (ms)	391 (24)	396 (26)	0.245
Minimum QT (ms)	295 (25)	299 (23)	0.227
Maximum QT (ms)	358 (25)	365 (23)	**0.046**
QT dispersion (ms)	63 (21)	66 (21)	0.432
Left ventricular systolic functions			
Ejection fraction (%)	71.1 (5.1)	69.1 (4.7)	0.084
Shortening fraction (%)	39.8 (4.3)	38.1 (3.7)	0.098

QTc = corrected QT interval
Values are expressed as mean with standard deviation given in parentheses
p-value <0.05 was considered statistically significant

however, these changes were not statistically significant – $p = 0.486$, 0.802, and 0.097, respectively.

Maximum QT interval after 5 weeks of therapy increased significantly when compared with the baseline value ($p = 0.046$). Minimum QT, corrected QT interval, and QT dispersion values after 5 weeks of therapy increased when compared with baseline values, but were not statistically significant – $p = 0.227$, 0.245, and 0.432, respectively.

Ejection fraction and shortening fraction values on 5 weeks of therapy decreased when compared with the baseline values – $p = 0.084$ and 0.098, respectively.

Discussion

This study demonstrates that, in children with attention deficit/hyperactivity disorder without structural cardiac disease, short-term atomoxetine treatment did not cause statistically significant alterations on QT dispersion and left ventricle systolic functions. To our knowledge, the effects of atomoxetine on QT dispersion and left ventricle systolic functions have not been reported previously.

Prolongation of corrected QT interval, whether congenital or acquired, may cause ventricular arrhythmias, particularly, torsades de pointes, syncope, and sudden death.[12] Increases in corrected QT interval greater than 30 milliseconds, or absolute corrected QT interval exceeding 500 milliseconds, are predictive for the development of drug-induced torsades de pointes.[13]

Data from Spencer et al[14] revealed no evidence of effects of atomoxetine on corrected QT interval, PR, and QRS intervals; mean conduction; or repolarisation time. Moreover, Kratochvil et al[15] found no statistically or clinically significant changes in corrected QT interval with the use of atomoxetine. However, Allen et al[16] reported a decrease in corrected QT interval in the atomoxetine-treated group. Evidence for the lack of an effect of atomoxetine on increasing the corrected QT interval is supported by Wernicke et al[3] who found no evidence of a prolonged QT interval during 1 year of treatment. All patients in our study group were asymptomatic, with no signs of arrhythmia. Atomoxetine caused a slight prolongation of the corrected QT interval – from 391 plus or minus 24 milliseconds to 396 plus or minus 26 milliseconds – without causing increased heterogeneity of repolarisation, and the clinical significance of this prolongation is unclear. However, the results of our study suggest that a potential risk of arrhythmia due to atomoxetine should be taken into consideration to reduce the risk substantially.

The standard distribution for QT dispersion is not well defined in normal individuals, although 30–60 milliseconds is generally considered normal.[17,18] Results vary widely, and measurements in healthy subjects as low as 11 milliseconds and as high as 71 milliseconds have been reported.[19,20]

QT dispersion is an indirect measure of the heterogeneity of ventricular depolarisation.[21] Previous studies showed that increased QT interval dispersion is associated with an increased risk of malignant ventricular arrhythmias and sudden death.[4,21,22] In our study, we used QT dispersion as markers of ventricular repolarisation inhomogeneity. Atomoxetine mildly increased QT dispersion from 63 plus or minus 21 milliseconds to 66 plus or minus 21 milliseconds, but were not significantly different from the baseline values. We found no evidence of increased heterogeneity of repolarisation in our study group. The results of our

https://doi.org/10.1017/S1047951111001211 Published online by Cambridge University Press

study suggest that atomoxetine has no significant effect on QT dispersion after 5 weeks of therapy.

Wernicke et al[3] assessed the short-term cardiovascular effects of atomoxetine in three studies of up to 10 weeks' duration.[23,24] They concluded that there was a statistically significant increase in heart rate in children receiving atomoxetine compared with placebo. Donnelly et al[25] showed a statistically significant decrease in heart rate from baseline to endpoint in patients treated for more than 3–4 years. They remarked that the decrease in heart rate is consistent with decreases in healthy individuals. In our study, systolic and diastolic blood pressure were found to be mildly lower after 5 weeks of treatment; heart rate values were also mildly slowed when compared with the baseline value, but did not differ statistically significantly.

Left ventricle systolic functions by echocardiography in patients taking atomoxetine have not been studied previously. In our study, echocardiography enabled both ruling out of underlying structural cardiac disease, which may have an effect on electrocardiography, and evaluation of left ventricle systolic functions. After atomoxetine treatment, ejection fraction and shortening fraction mildly decreased but were not significantly different from baseline values.

Conclusion

The results of this study suggest that atomoxetine does not cause statistically or clinically significant alterations in QT dispersion, systolic and diastolic blood pressure, heart rate, corrected QT interval, and left ventricular systolic functions during short-term treatment in children with attention deficit/hyperactivity disorder. Cardiovascular effects of atomoxetine were minimal, and atomoxetine was well tolerated in this short-term study. Double-blind, randomised, placebo-controlled future studies are needed to confirm this.

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