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QTc prolongation after ADHD medication

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Abstract

OBJECTIVE: Multicenter studies have shown that cardiovascular risks of ADHD medication are extremely low. However, QTc length has been shown to be increased in smaller samples of patients or case reports after stimulant and atomoxetine medication. Based on recent studies of genetic polymorphisms associated with drug-induced QTc prolongation and polymorphisms linkage to regional populations, we hypothesized that the drug-induced QTc prolongation could be a factor of particular polymorphisms linked to specific regional populations undistinguished in multicenter studies.
METHODS: We included 69 patients from a region of central Slovakia, 36 patients were taking atomoxetine and 33 patients methylphenidate. QTc, heart rate, potassium levels and BMI were examined before and after 8 weeks of treatment. Therapeutic effect was measured by ADHD-RS-IV.
RESULTS: We found QTc prolongation after 8 weeks of treatment both with atomoxetine and methylphenidate that was neither followed by the significant changes in BMI and potassium levels nor the significant increase of heart rate.
CONCLUSION: This is the first study revealing QTc prolongation in the group of ADHD children from the same region after 8-week treatment with atomoxetine and methylphenidate, indicating the potential discrete abnormalities in cardiac functioning associated with polymorphisms in genes of dopaminergic and noradrenergic system.

ORIGINAL ARTICLE

INTRODUCTION

A stimulant drug methylphenidate and a non-stimulant atomoxetine are worldwide approved for ADHD treatment. These drugs have not been associated with severe cardiovascular events including clinically or statistically significant prolongation of corrected QT interval in large clinical or population-based studies as comprehensively rewieved in Martinez-Raga *et al.* 2013 (Martinez-Raga et al. 2013). However, QTc lenght has been shown to be increased in smaller samples of patients or case reports after stimulant (Ari 2014; Connor 2005) and atomoxetine (Yamaguchi et al. 2014) medication respectively.

The QT interval is a measure of the time between the beginning of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened

QT interval is a marker for the potential of ventricular tachyarrhythmia, such as torsades de pointes, and a risk factor for sudden death (Panicker *et al.* 2014). The QT interval is obviously dependent on the heart rate and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia.

Cardiovascular risk is also associated with other factors, such as increasing age, male sex, anthropometric parameters, pro-arrhythmic drugs (e.g. tricyclic antidepressants) and with conditions, such as hypokalaemia, hypothermia, and congenital long QT syndrome (Ptacek *et al.* 2009; Kozar *et al.* 2015; Brat *et al.* 2015). Recent studies repeatedly reported prolongation of the QTc interval with increasing body mass index (BMI) and intra-abdominal fat. Therefore, studies observing changes in QTc intervals should consider levels of potassium and body mass index in relation to the prolongation of QTc intervals (Park 2005; Wojcik *et al.* 2015).

The growing evidence has revealed that the specific polymorphisms contribute to the length of QTc (Aziz *et al.* 2013; Gouas *et al.* 2005; Grandinetti *et al.* 2006; Paavonen *et al.* 2007; Friedlander *et al.* 2005; Bezzina *et al.* 2003; Kauppila *et al.* 2013; Nof *et al.* 2010; Mints *et al.* 2014), moreover a recent study has found the association between a particular polymorphism of gene included in metabolism of risperidone and risperidone-induced QTc prolongation in patients with schizofrenia (Suzuki *et al.* 2014). As it has been shown in family-based association analyses in an isolated Mongolian and Israeli populations, the heritability component of QTc lenght is 0.31 and 0.33 respectively (Im *et al.* 2009; Friedlander *et al.* 2005). We hypothesized that the drug-induced QTc prolongation in ADHD patients medicated by atomoxetine or stimulants could be a factor of a particular polymorphisms that could be linked to a specific regional populations undistinguished in the large multicenter studies. Therefore, we decided to examine the QTc response to atomoxetine and methylphenidate in the small sample of children patients with ADHD from a relatively small region of central Slovakia after 8 weeks of treatment. Body mass index and potassium plasma concentrations were examined to exclude their effects on QTc length after medication.

MATERIALS AND METHODS

Subjects

We recruited 93 patients with the diagnosis of ADHD in the age of 5–16 years. All recruited children were in-patients of the Department of Child and Adolescent Psychiatry, Clinic of Psychiatry, University Hospital in Martin, between January 2011 and June 2014. All patients were of Caucasian origin living in the region of central Slovakia. All patients met diagnostic criteria for attention deficit/hyperactivity disorder – combined type, based on the Diagnostic & Statistical Manual of Mental Disorders DSM-IV-TR (Text Revision). All patients were diagnosed by two independent child psychiatrists using clinical examination and the ADHD rating scale IV revision (ADHD-RS-IV), which had the supportive diagnostic value. ADHD-RS-IV was used to evaluate the treatment effects prior to and after 8 weeks of treatment. The study was approved by the Ethics Committee of Jessenius Medical Faculty, Comenius University, Martin, Slovak republic. All procedures performed in our study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All children/patients/guardians were carefully informed about the study protocol and written informed consent was obtained from them to participate in the study prior to examination.

Exclusion criteria were other psychiatric and paediatric diagnoses, a medical history of cardiovascular abnormalities, previous treatment with atomoxetine, methylphenidate or other psychiatric drugs as well as other drugs known to influence the cardiovascular system (heart rhythm, blood pressure, and electrocardiogram), electrolyte abnormalities, weight abnormalities, smoking, a different race, IQ lower than 70 and low degree of ADHD symptoms.

Recruited patients were randomised into two groups. The first group consisted of 48 patients (35 boys, 13 girls) treated with atomoxetine. The second group consisted of 45 patients with ADHD (34 boys, 11 girls) treated with methylphenidate, retard capsules. We followed the generally recommended dosage according to the U.S. Food and Drug Administration (FDA). In children and adolescents weighing up to 70 kg, atomoxetine was initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg. Both were administered as a single daily dose in the morning. In children and adolescents weighing over 70 kg, the drug was initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg. Both were administered as a single daily dose in the morning. Methylphenidate was initiated with 10 mg once a day. Doses were increased weekly of 10 mg according to the clinical symptoms until a maximum of 40 mg/day in one dose.

During the 8-week period, 24 patients discontinued from the study due to non-compliance to treatment or adverse effects. Sixty-nine patients (54 boys, 15 girls; 11±0.3 years) finished the study and were included into the statistical evaluations. Thirty-six patients (27 boys, 9 girls) aged 5–16 years (10.5±0.5yr) were taking atomoxetine and 33 patients (27 boys, 6 girls) aged 5–16 years (10.6±0.5 yr) were treated with methylphenidate.

QTc analysis

All patients underwent electrocardiography examination before and after 8 weeks of medication. All

QT interval measurements were performed from the 12-lead standard ECG (MAC 1200 ST, ECG Professionals™, United States of America) recorded at a paper speed of 25 mm/s. ECG recordings were blindly analysed in all patients by two independent cardiologists. Heart rate, QT, and corrected QT (QTc) were calculated in four successive complexes for each lead. 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 T waves were inverted, the end was taken at the point where the trace returned to the T-P baseline, and when U waves were present, the end of the T wave was taken as the nadir between the T and U waves (Barr *et al.* 1994). The QT interval was corrected for heart rate using Bazett's formula (HC 1920).

Potassium analysis

Blood was taken in the morning in a fasting state and placed in EDTA test-tubes. Potassium analyses were performed before and after 8 weeks of medication by the ion selective electrodes module on an Olympus AU640 analyser (Beckman Coulter Inc., Brea, California, United States of America) in the Biochemical laboratory at the University Hospital in Martin.

Body mass index

Body weight and height were measured by standard methods before and after 8 weeks of medication. Measurements were calculated according to the formula: BMI = weight (kg)/height^2 (m^2). All values were reviewed with respect to age and gender according to percentile graphs for the Slovak population (Sevcikova L 2004).

Statistical analyses

QTc intervals, heart rate, potassium levels, BMIs and ADHD-RS-IV were statistically analysed by paired t-tests in both treatment groups. QTc length differences between groups prior to and after treatment were analysed by unpaired t-test. Post-hoc Bonferroni correction with adjustment of α was used to compensate the multiple testing effects. The significance level was set at $p<0.005$.

RESULTS

We found the statistically significant prolongation of QTc interval after 8 weeks of medication in both treatment groups (Figures 1 and 2). Heart rate slightly increased in both groups, but this difference was not statistically significant. Neither BMI nor potassium levels significantly differ before and after treatment. We found statistically significant decrease in ADHD-RS-IV score after treatment in both treatment groups (Tables 1 and 2). QTc length did not differ between treatment groups neither prior to nor after medication (p=0.676, p=0.196).

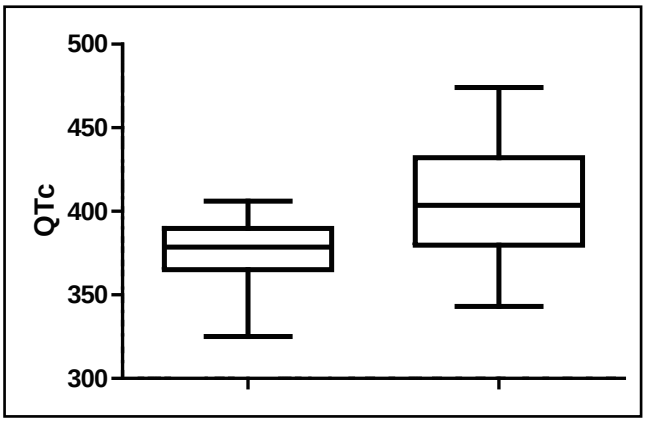

Fig. 1. QTc in miliseconds before and after atomoxetine treatment.

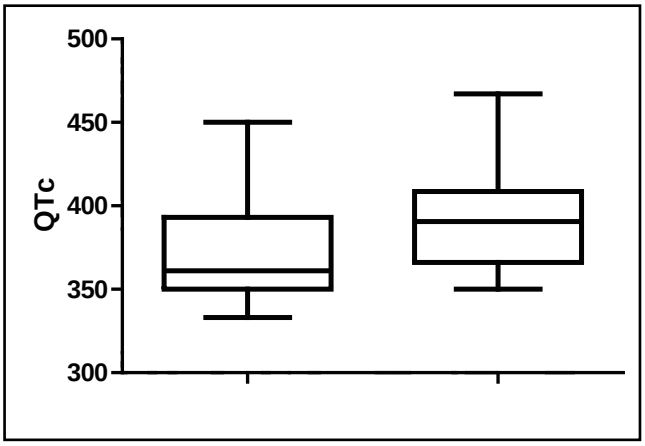

Fig. 2. QTc in miliseconds before and after methylphenidate treatment.

DISCUSSION

We found the QTc prolongation after 8 weeks of treatment both with atomoxetine and methylphenidate in children and adolescents with ADHD from central region of Slovakia. The QTc prolongation was neither followed by the changes in BMI and potassium levels nor the significant increase of heart rate. We found very statistically significant decrease in ADHD-RS-IV score after medication in both treatment groups.

The QTc is an indicator of ventricular depolarization and repolarization and prolongation in the QT interval is a risk factor for ventricular arrhythmias(Ari 2014). As concluded in an extensive review of cardiovascular risks during ADHD treatment, the risk for significant increases in QTc after stimulant or atomoxetine medication is extremely low, but caution is advised in patients with personal or family history or other known risk factors for cardiovascular disease (Martinez-Raga *et al.* 2013). However, the majority of the studies included in the review were multicenter with hundreds to thousands of patients, in which several patients with QTc prolongation could be undistinguished in statistical analyses. We propose that the small research of patients

Tab. 1. Measured parameters in the group treated with atomoxetine before and after treatment.

	Before		After		*p*-value
	mean	SD	mean	SD	
QTc (msec)	376	21.68	406.67	36.55	0.003*
HR (bpm)	83.78	13.22	85.56	14.27	0.510
BMI (kg/m^2)	16.92	12.68	15.95	12.66	0.819
Potassium (mmol/l)	4.10	0.94	4.28	0.31	0.387
ADHD-RS-IV	39.81	9.88	20.44	11.86	<0.0001*

QTc interval- corrected QT Interval, HR – heart rate, BMI – body mass index;ADHD-RS-IV – ADHD Rating Scale IV. Version; kg- kilogram; m- meter; bpm- *beats per minute*; mmol/l- millimol per litre, msec- millisecond; SD – standard deviation; *statistically significant result

Tab. 2. Measured parameters in the group treated with methylphenidate before and after treatment.

	Before		After		*p*-value
	mean	SD	mean	SD	
QTc (msec)	367.33	30.28	391.99	28.16	0.004*
HR (bpm)	78.52	16.52	81.59	12.54	0.642
BMI (kg/m^2)	19.15	3.26	19.10	3.20	0.230
Potassium (mmol/l)	4.24	0.34	4.25	0.31	0.076
ADHD-RS-IV	33.45	11.05	22.73	9.80	<0.0001*

QTc interval- corrected QT Interval, HR – heart rate, BMI – body mass index;ADHD-RS-IV – ADHD Rating Scale IV. Version; kg- kilogram; m- meter; bpm- *beats per minute*; mmol/l- millimol per litre, msec- millisecond; SD – standard deviation; *statistically significant result

from the same region could reveal what remains unknown in large multicenter studies. Moreover, the genetic risks for drug-induced QTc prolongation after medication are generally unknown till the present days.

To our best knowledge, this is the first study focused on QTc measure while including exclusively patients from the same small area. Based on recent findings of the association between a particular polymorphism of gene included in metabolism of a drug and drug-induced QTc prolongation (Suzuki *et al.* 2014) and the knowledge of the particular polymorphism`s regional binding, we hypothesized that the drug-induced QTc prolongation in ADHD patients after medication could be a factor of a particular polymorphisms that could be linked to a specific regional populations. We propose, that the underlying polymorphisms could be included in the genes involved in metabolism, pharmacokinetics or pharmacodynamics of medication. There are some studies supporting this hypothesis. A placebo-controlled study of the atomoxetine`s effects on the QT interval in healthy CYP2D6 poor metabolizers revealed a statistically significant increase in QTc with increasing atomoxetine plasma concentrations (Loghin *et al.* 2013). Furthermore, the findings of the recent studies could explain the genetic mechanisms included in pharmacodynamic actions of atomoxetine and methylphenidate. As atomoxetine has blocked the current of the opened potassium ion channels encoded by hERG gene (Scherer *et al.* 2009) and the polymorphism within hERG gene has been associated with the susceptibility to drug-induced QT-prolongation (Bezzina *et al.* 2003), the QTc prolongation after atomoxetine medication could appear only in people having this polymorphism. Atomoxetine could affect QT interval also through its adrenergic effects (Paclt *et al.* 2005), as beta1-adrenergic receptor polymorphisms have been associated with the risk of symptoms in type 1 of long QT syndrome (Paavonen *et al.* 2007). A pharmacogenetic study of ADHD children has revealed that children possessing the 7-repeat allele of the dopamine D4 receptor gene require higher doses of methylphenidate for symptoms` management (Hamarman *et al.* 2004), that could hypothetically lead to more extensive sympathomimetic effects. However, contrary to atomoxetine (Sawant & Daviss 2004), methylphenidate overdose in study of adults (Hill *et al.* 2010) or adolescent case reports (Klampfl *et al.* 2010; Ozdemir *et al.* 2010) has not lead to QTc prolongation. Thus, it is not probable that the polymorphism of DRD4 gene alone could result in QTc increase after methylphenidate overdose. However, higher doses of methylphenidate in people possessing the two of the above mentioned polymorphisms in DRD4 gene (Hamarman *et al.* 2004) and beta1-adrenergic receptor gene (Paavonen *et al.* 2007) could have potential fatal consequences.

As we did not evaluate any of the above mentioned polymorphisms, the reason of the significant QTc prolongation in children with ADHD from Slovakia remains in question. Further studies evaluating the associations of medication-induced QTc prolongation with the polymorphisms in candidate genes are necessary to assess the potential genetic risks.

We found the significant decrease of the total score of ADHD-RS-IV, thus patients in our study were predominantly good responders to treatment. The majority of the patients who were non-responders to medication did not have the good compliance to treatment and droped from the study. Recent studies have shown that responsivity to methylphenidate is associated with polymorphisms in genes of brain-derived neurotrophic factor (Kim *et al.* 2011), carboxylesterase 1 (Nemoda *et al.* 2009) and dopamine transporter (Contini *et al.* 2013). Response to atomoxetine is connected with polymorphisms in adrenergic neurotransmitter system transporter and receptor genes (Yang *et al.* 2013) and noradrenergic transporter gene (Ramoz *et al.* 2009). As the QTc lenght after medication could be associated with polymorphisms in genes for dopamine receptor (Hamarman *et al.* 2004) and beta1-adrenergic receptor (Paavonen *et al.* 2007), future studies should

evaluate the potential risks of medication-induced QTc prolongation connected to gene-associated responsivity to treatment.

In spite of the fact that we revealed the statistically significant increase of QTc interval in our group of patients with ADHD, any of the patients did not exceed the physiological limit of QTc. The clinical relevance of our results could be prominent in interactions with other drugs affecting QTc lenght, and somatic factors such as dehydratation and mineral dysbalancies. In these situations the QTc could be prolonged at the pathological levels and could increase the risk of arrhytmias.

This is the first study evaluating the medication-induced QTc prolongation in the regionally-linked small group of children with ADHD. We revealed that the QTc intervals were prolonged in the group of ADHD patients from small region of central Slovakia after 8-week treatment both with atomoxetine and methylphenidate. Our results indicate the potential discrete abnormalities in cardiac functioning associated with polymorphisms in genes of dopaminergic and noradrenergic system. Research of genetic polymorphisms associated with QTc susceptibility to medication-induced prolongation is needed.

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