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Original Article

Evaluation of Cardiovascular Effects of Methylphenidate in Children with Attention-deficit Hyperactivity Disorder

Çocuklarda Dikkat Eksikliği ve Hiperaktivite Bozukluğunda Metilfenidatın Kardiyovasküler Etkilerinin Değerlendirilmesi

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ABSTRACT

Objective: In patients with attention-deficit hyperactivity disorder (ADHD), methylphenidate (MPH) treatment may lead to serious cardiac problems. Therefore, this study was undertaken to assess cardiac effects and electrocardiographic (ECG) changes regarding risks of ventricular arrhythmia occurring after initiation of MPH treatment in ADHD patients.

Method: Thirty patients (mean age: 8.9±1.93 years) diagnosed with ADHD and 41 healthy subjects (mean age: 9.78±3.07 years) were included in this study blood pressures, heart rates, and ECGs of the patients were evaluated before and third month of treatment. ECG parameters including QRS, QT, corrected QT interval (QTc), QTdispersion (QTdis), Tp-Te, Tp-Te dispersion, and Tp-Te/QTc ratio were also assessed.

Results: Untreated patients with ADHD and healthy subjects had similar systolic blood pressures and heart rates, although ADHD patients had higher diastolic blood pressures. An increase in heart rates, systolic and diastolic blood pressures was observed in the patient group in third month of treatment. Prior to MPH treatment, patients with ADHD and control subjects were compared in terms of ECG parameters: QRS, QT, QTc, QTdis, Tp-Te, Tp-Te dispersion, Tp-Te/QTc ratio but without any intergroup difference. Following MPH treatment, QRS, QT, QTc, QTdis did not change in the patient group but significant increases were observed in Tp-Te, Tp-Te dispersions, Tp-Te/QTc ratios.

Conclusion: Use of the MPH in ADHD patients is associated with alterations in ECG parameters, heart rates, diastolic and systolic blood pressures. Assessment of ECG parameters such as Tp-Te, Tp-Te dispersions, Tp-Te/QTc ratios may prove more beneficial for evaluating the risk of ventricular arrythmia in pediatric patients with ADHD.

Keywords: Attention-deficit hyperactivity disorder, electrocardiography, methylphenidate

ÖZ

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan hastalarda, metilfenidat (MPH) tedavisi ciddi kardiyak problemlere yol açabilmektedir. Bu yüzden çalışmamız da DEHB tanısı alan ve MPH tedavisi başlanılan hastalarda tedavi öncesi ve sonrasında kardiyak etkileri ve ventriküler aritmi açısından elektrokardiyografik (EKG) değişiklikleri değerlendirmeyi amaçladık.

Yöntem: Çocuk ve ergen psikiyatrisi kliniğinde DEHB tanısı koyulan 30 hasta (yaş ort: 8,9±1,93 yıl) ve 41 sağlıklı kontrol (yaş ort: 9,78±3,07 yıl) çalışmamıza dahil edildi. Kontrol ve hasta grubunun tedavi öncesi ve tedavinin üçüncü ayında kan basıncı, kalp hızı ve EKG, sonuçları kaydedildi. EKG incelemesinde QRS, QT, QTc, QTdispersiyon (QTdis), TpTe, TpTe dispersiyon ve TpTe/QTc oranı belirlendi.

Bulgular: DEHB olan hastaların tedavi öncesi ile kontrol grubu karşılaştırıldığında; sistolik kan basıncı ve kalp hızı arasında fark yok iken, diyastolik kan basıncı daha yüksek idi. DEHB tanılı hastalarda 3 aylık MPH tedavisi sonrasında; kalp hızı, sistolik ve diyastolik kan basıncında artış izlendi. Kontrol grubu ve tedavi öncesi DEHB olan hasta grubu, EKG parametreleri açısından karşılaştırıldığında; QRS, QT, QTc, QTdis, TpTe, TpTe dispersiyon ve TpTe/QTc oranı arasında anlamlı farklılık yoktu. Tedavi sonrasında ise TpTe, TpTe dispersiyon, TpTe/QTc oranında anlamlı artış olduğunu, ancak QRS, QT, QTc, QTdis değerlerinde değişiklik olmadığını izledik.

Sonuç: DEHB olan hastalarda MPH kullanımının EKG üzerinde etkisi olabilmektedir. Bu nedenle tedavi öncesi ve ilaç kullanımını takiben EKG parametreleri çok dikkatli takip edilmelidir. Bu hastaların takibinde ventriküler aritmi açısından TpTe, TpTe dispersiyonu ve TpTe/QTc oranı gibi yeni belirteçlerin kullanılması faydalı olacaktır.

Anahtar kelimeler: Dikkat eksikliği ve hiperaktivite bozukluğu, elektrokardiyografi, metilfenidat

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a multifactorial disorder accompanying age-inappropriate behaviors. These patients show increased hyperactivity, inattention, and impulsive behaviors [1]. Prevalence of the ADHD is between 2% and 7% with an average of around 5 percent [2].

The aim of treatment in ADHD patients is to get better functioning in behavioral, social and cognitive domains [3]. Methylphenidate (MPH) is a psychostimulant agent with sympathomimetic effects and the most commonly prescribed pharmacological treatment for ADHD [4]. MPH exerts its sympathomimetic effects through inhibition of catecholamine reuptake and elevation of dopamine and noradrenaline levels in the central nervous system. These sympathomimetic effects have been reported to cause various side effects, such as increases in systolic and diastolic blood pressures as well as pro-arrhythmic effects [5,6]. Thus, patients should be referred for early cardiological assessment in order to identify high-risk individuals.

Use of surface electrocardiography (ECG) and determination of ventricular repolarization heterogeneity may allow identification of high-risk patients. Several ECG parameters including QT interval, corrected QT interval (QTc) and QT dispersion (QTdis) have been used to evaluate the ventricular repolarization heterogeneity, although QT interval, QTc and QTdis are frequently insufficient to determine ventricular repolarization. The T wave in ECG reflects ventricular repolarization, and interval from the peak to the end of the T wave (Tp-Te interval) reflects the dispersion of ventricular repolarization [7,8]. Prolongation of the Tp-Te interval on the 12-lead ECG may indicate a new marker of ventricular arrhythmogenesis [9].

In ADHD patients, MPH treatment may lead to serious cardiac problems. Therefore, this study was undertaken to assess cardiac effects and ECG changes regarding risks of ventricular arrhythmia occurring after initiation of MPH treatment in ADHD patients.

MATERIALS and METHODS

Study Population

This study was conducted between January 01, 2018 and December 31, 2019 and included patients diagnosed with ADHD in the child and adolescent psychiatry clinic. Diagnosis of ADHD was made by child and adolescent psychiatrists according to the DSM-5 criteria [10]. Patients with ADHD who were to be started on drug therapy were evaluated by pediatric cardiology before treatment with MPH. Blood pressures, heart rates, echocardiographic, and ECG parameters of the patients scheduled to receive drug therapy were evaluated before and third month of treatment.

Treatment was started with daily doses of 5 mg MPH and titrated in a month until the therapeutic dose was achieved. The minimum and maximum doses were 5 mg and 40 mg, respectively, and the dose was individualized for each child according to his/her weight.

Age-matched subjects attending to our cardiology outpatient unit for the assessments of cardiac murmurs or for obtaining a health status report to join sports activities comprised the control group, provided that they had no cardiac defects or arrhythmia.

Exclusion criteria included presence of cardiac disease, drug usage which may prolong the QT interval (betamimetics, antihistamines, etc.), electrolyte disorders, and presence of the pulmonary or endocrine disorders.

A written approval was obtained from the Buca Seyfi Demirsoy Training and Research Hospital Non-interventional Research Ethics Committee before this study (decision no: 2021/7-56, date: 28.07.2021) and informed consent was received from all individual participants included in the study.

Electrocardiography

Twelve-lead ECG was taken under similar conditions from patients and the control group. Biocare 12A ECG device was used for ECG recordings at standart velocity and amplitude.

QRS interval was calculated as the time elapsed between the onset of the Q wave to the end point of S wave and the averaged measurements were obtained from all leads.

Duration of QT interval was calculated in leads DII, V5, and V6 and defined as the mean time from the starting point of QRS complex to the end point of T wave on the isoelectric line. We used Bazett's correction formula to measure the QTc interval for heart rate: ($QTc = QT/\sqrt{RR}$ in seconds). QTd was defined, and calculated as the difference between the minimum and maximum QT intervals of the 12 lead ECG. In addition, heart rates, Tpeak-Tend (Tp-Te) intervals, Tp-Te dispersions,

and Tp-Te/QTc ratios were calculated. Tp-Te intervals were measured with the tangent method in precordial leads [9]. A tangential line was drawn where the downward curve of the T wave intersected the isoelectric line. The Tp-Te intervals were calculated by measuring the distance between the two points on the isoelectric line. The difference between the maximum and minimum Tp-Te values in the precordial leads was defined as the Tp-Te dispersion. Systolic and diastolic blood pressures and heart rates were recorded for all groups.

Statistical Analysis

Statistical Package for the Social Sciences version 23 (SPSS Inc, Chicago, IL) was used for data analysis. The Shapiro-Wilk test was used to test for normality. Data with normal and non-normal distribution were examined using the independent t-test, and the Mann-Whitney U test, respectively. Chi-square test was performed to compare categorical variables. The comparisons were made using One-Way ANOVA. Then, post-hoc Tukey and Tamhane's T2 test were used to evaluate multiple comparisons. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 30 patients diagnosed with ADHD (18 males, 12 females, mean age 8.9±1.93 years), and 41 healthy subjects (25 males, 16 females, mean age: 9.78±3.07 years) were included in this study. Study groups did not differ significantly regarding age and gender ($p>0.05$).

ADHD patients were receiving MPH treatment for at least 3 months at daily doses ranging between 5 and 40 mg. Both ADHD patients and healthy controls had normal echocardiography findings. Before initiation of treatment, ADHD patients and healthy controls had comparable systolic blood pressures and heart rates, although ADHD patients had higher diastolic blood pressures (67.83±3.21 mmHg vs. 65.17±5.07 mmHg; $p=0.014$). At the third month of treatment increases in systolic blood pressures (106.63±6.01 vs. 102.1±7.1 mmHg; $p=0.049$), diastolic blood pressures (70.30±4.69 vs. 67.83±3.21 mmHg; $p<0.001$), and heart rates (82.23±6.14 vs. 77.60±6.69 : beat per minute; $p=0.025$) were observed in the patient group. The demographic and clinical findings of the patient and healthy control groups are shown in Table 1.

Electrocardiographic Results

Prior to MPH treatment, patients with ADHD and control subjects were compared in terms of ECG parameters: QRS, QT, QTc, QTdis, Tp-Te, Tp-Te dis intervals, and Tp-Te/QTc ratios and any intergroup difference was not observed. Following MPH treatment,

Table 1. Comparison of demographic findings, blood pressure and heart rates values of the patient and the healthy control groups

	Healthy control group n=41	Patients with ADHD n=30		p-value
		pre-MPH treatment	post-MPH treatment	
Age (year) Mean ± SD	9.7±3.07	8.9±1.93	-	0.17
Gender F (n, %) M (n, %)	16 (39%) 25 (60%)	12 (40%) 18 (60%)	-	0.93
Systolic BP (mmHg) Mean ± SD	101.3±8.35	102.1±7.1	106.6±6.01[a,b]	0.011[a] 0.049[b]
Diastolic BP (mmHg) Mean ± SD	65.1±5.07	67.8±3.21 [a1]	70.3±4.69[a2,b]	0.014[a1] <0.001[a2] <0.001[b]
Heart rate Mean ± SD	75.3±7.25	77.6±6.69	82.2±6.14[a,b]	<0.001[a] 0.025[b]

Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, ADHD: Attention-deficit hyperactivity disorder, MPH: Methylphenidate, SD: Standard deviation, F: Female, M: Male

[a]Different from the healthy control group ($p<0.05$)

[a1]Different from the healthy control group ($p<0.05$)

[a2]Different from the healthy control group ($p<0.05$)

[b]Different from the untreated ADHD group ($p<0.05$)

QRS duration, QT intervals, QTc, and QTdis did not change significantly in the patient group (p>0.05) although a statistically significant increase in Tp-Te intervals, TpTe dis, and Tp-Te/QTc ratios was found. ECG results of the patient and the healthy control groups are shown in Table 2.

DISCUSSION

Psychostimulant agents, such as MPH, represent the mainstay of pharmacological treatment in ADHD, with class 1 evidence showing their efficacy in this condition [11,12]. However, potential side effects of these agents remain a significant concern. While a large retrospective study did not report any cardiac side effects due to MPH use [13], another prospective study reported increased risks of arrhythmia, cerebrovascular events, and hypertension at rates of 23%, 9%, and 8%, respectively [14]. On the other hand, studies evaluating the cardiovascular effects, and particularly ventricular arrhythmogenic effects of psychostimulants in pediatric patients are limited in number [15-17]. Our study represents one of the few studies examining the effect of MPH treatment on ADHD patients in comparison with healthy subjects. According to our results, although ECG parameters did not differ significantly between ADHD patients and healthy controls prior to treatment, significant increases in Tp-Te intervals, Tp-Te dis, and Tp-Te/QTc ratios as well as systolic and diastolic blood pressures were observed following drug therapy in the MPH group, without any significant changes in QTdis, QTc, and QT intervals.

Tp-Te interval, Tp-Te dispersion and Tp-Te/QTc ratio are among the new trans-myocardial repolarization parameters that define trans-myocardial heterogeneity [9,18]. Amplification of trans myocardial heterogeneity or ventricular repolarization dispersion has long been known to be a substrate for ventricular arrhythmias [9]. In particular, the Tp-Te/QTc ratio serves as a more precise index of arrhythmogenesis, as it provides an estimate of the repolarization dispersion relative to the total repolarization time [9]. In Lamberti et al.'s [15] study examining the acute effects of MPH, any significant differences were not detected between measurements of the acquired Tp-Te intervals, while post-treatment Tp-Te/QTc ratios, though within the normal range, increased compared to the baseline values. However, in contrast with our findings, these authors observed these parameters for only 2 hours following MPH treatment, ECG findings during the long-term follow-up of the patients were not investigated. Another study reported increases in Tp-Te, Tp-Te dis, and Tp-Te/QTc ratios after 3 months of MPH treatment. Similarly, while there were no significant differences between ADHD patients and healthy controls before treatment, post-treatment increases were noted in Tp-Te intervals, Tp-Te dispersions and Tp-Te/QTc ratios among ADHD

Table 2. Comparison of the electrocardiographic parameters between the patient and the healthy control groups

ECG parameters	Healthy control group n=41	Patients with ADHD n=30		p-value
		pre-MPH treatment	post-MPH treatment	
QRS (ms) Mean ± SD	75.21±8.42	77.33±7.54	81.33±7.76[a]	0.007[a]
QT (ms) Mean ± SD	345.80±29.52	358.50±28.04	368.33±13.97[a]	<0.001[a]
QTc (ms) Mean ± SD	390.17±21.55	393.87±16.20	402.17±12.64[a]	0.014[a]
QTc dis Mean ± SD	27.92±8.28	31.83±9.60	32.66±5.83[a]	0.018[a]
Tp-Te (ms) Mean ± SD	72.07±9.41	76.00±8.44	92.67±6.91[a,b]	<0.001[a] <0.001[b]
Tp-Te dispersion (ms) Mean ± SD	10.78±3.84	11.80±2.70	14.83±3.43[a,b]	< 0.001[a] 0.001[b]
TpTe/QTc (ms) Mean ± SD	0.18±0.029	0.19±0.02	0.22±0.019[a,b]	<0.001[a] <0.001[b]

[a]Different from the healthy control group (p<0.05)

[b]Different from the untreated ADHD group (p<0.05)

ADHD: Attention-deficit hyperactivity disorder, MPH: Methylphenidate, SD: Standard deviation, ECG: Electrocardiography

patients [16]. In a large series where the cardiovascular safety among 1,224 patients was evaluated, increased risk of arrythmia, particularly in children with congenital cardiac problems was noted , without any increased risk in other conditions such as myocardial infarction or heart failure [19].

QT represents the interval between the beginning of the Q wave and the end of the T wave and therefore corresponds to ventricular depolarisation and repolarisation. Increased QT, QTdis and QTc intervals are important markers of heterogeneous myocardial repolarization, but they do not always accurately reflect the risk of polymorphic ventricular tachycardia and sudden cardiac death. It has been suggested that a QTc interval higher than 500 ms, and a QTdis interval higher than 100 ms increase the risk of arrhythmia [20]. The QTc interval was not higher than 500 ms and the QTd interval was not higher than 100 ms in any of our patients before and after the treatment. Türkmenoğlu et al. [17] reported no changes in QTc and QTdis intervals following 1 month of MPH treatment. Similarly, MPH treatment was not associated with QTdis, QTc, and QT intervals in our study. Arcieri et al. [6] compared MPH and atomoxetine treatments in children with ADHD, and found that five patients who received MPH had slightly prolonged QTc intervals after six months of drug therapy, but values remained within normal levels. In another study evaluating the acute effects of MPH treatment, Lamberti et al. [15] identified no change in QT, QTc, and QTdis, concluding that this treatment was safe in children.

An increase in heart rate and blood pressure measurements has been previously reported for psychostimulant agents, including MPH [21]. Some other studies in pediatric patients provided similar data [6,15]. In line with these previous observations, systolic and diastolic blood pressures and heart rates increased following MPH treatment in our patient group. In a study, patients receiving MPH were found to have higher blood pressures as compared to controls and ADHD patients who did not receive MPH treatment [16]. Another meta-analysis found that psychostimulants administered for the treatment of ADHD were associated with increased blood pressures and heart rates in all age groups tested [22]. An additional finding in our study was the observation that patients diagnosed with ADHD had significantly higher diastolic blood pressures than controls, even before treatment. Furthermore, these patients experienced slight, and non-significant elevations in their heart rates before treatment. These observations suggest that ADHD patients may have a low level of parasympathetic tone accompanied by a lack of physiological maturation of autonomic function [23].

Study Limitations

The small sample size was the most important limitation of our study. Another limitation of our study is the lack of evaluation with Holter ECG. We believe that further studies with larger sample size and longer follow-up periods are required for safe use of medicines in pediatric patient populations.

CONCLUSION

MPH, a psychostimulant agent used to treat ADHD, had certain effects on ECG parameters used to assess predisposition to ventricular arrhythmia as well as on diastolic, systolic blood pressures and heart rates. Appropriate therapeutic doses of this agent have not been associated with serious cardiovascular effects or fatal arrhythmic effects. However, this assumption does not negate the need to carefully evaluate ECG parameters both before and during treatment in this patient group. Particular care should be taken for children with prolonged QT intervals at baseline ECG. In addition to baseline ECG parameters, other predictive factors assessing the risks of arrhythmia such as TpTe, TpTe dispersion and TpTe/QT ratio, may be useful in pediatric ADHD patients.

Ethics

Ethics Committee Approval: A written approval was obtained from the Buca Seyfi Demirsoy Training and Research Hospital Non-interventional Research Ethics Committee before this study (decision no: 2021/7-56, date: 28.07.2021).

Informed Consent: Informed consent was received from all individual participants included in the study.

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Author Contributions

Concept: A.Ş., E.A., Design: A.Ş., E.A., Data Collection and/or Processing: A.Ş., E.A., E.G., Analysis and/ or Interpretation: A.Ş., M.A., Literature Search: A.Ş., E.A., E.G., M.A., Writing: A.Ş.

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