

## Early Cardiovascular Evaluation after Methylphenidate in Children with Attention-Deficit Hyperactivity Disorder

Dikkat Eksikliği ve Hiperaktivite Bozukluğu olan Çocuklarda Metilfenidat Tedavisi Sonrası Erken Kardiyovasküler Değerlendirme

Erman Cilsal<sup>1</sup>, Eray Yurtcu<sup>2</sup>, Aygül Elatas<sup>2</sup>

<sup>1</sup>Department of Pediatric Cardiology, Adana City Hospital, Adana, Turkey

<sup>2</sup>Department of Pediatrics, Adana City Hospital, Adana, Turkey

### ABSTRACT

**Objective:** Rare cardiovascular side effects may be observed in patients after treatment with methylphenidate for Attention Deficiency and Hyperactivity Disorder (ADHD). In this study, we aimed to evaluate the cardiac effects of methylphenidate before and after treatment in our center in children with ADHD.

**Method:** This study included 253 ADHD patients who underwent methylphenidate treatment and involved a retrospective comparison of their demographic data, heart rate, systolic, diastolic blood pressure, corrected QT (QTc) interval with electrocardiography and echocardiographic examinations from before and two weeks after treatment.

**Results:** The median age of the patients was  $11.8 \pm 3.3$  years, palpitations were observed in 18 (7%) patients, and blood pressure elevation was observed in 5 (1.9%) patients after methylphenidate treatment. Sinus tachycardia was observed in all patients with palpitation symptoms, and echocardiography revealed an atrial septal defect in four patients, valvular pulmonary stenosis in two patients, ventricular septal defect and patent ductus arteriosus in one patient. No significant difference in heart rate, systolic and diastolic blood pressure values were identified after treatment. Although the QTc intervals recorded after treatment were significantly longer, these values did not exceed pathological levels.

**Conclusion:** The findings of evaluations of children with ADHD after methylphenidate treatment vary according to the characteristics of the patients. Patients with structural heart disease or with arterial hypertension should be monitored more carefully before the use of methylphenidate in the diagnosis of ADHD. Our findings suggests that both blood pressure measurement and electrocardiographic assessment appear to be useful and appropriate in the detection of side effects after methylphenidate treatment.

**Key Words:** Attention deficit hyperactivity disorder, methylphenidate, structural heart disease, electrocardiography, hypertension, arrhythmia

Received: 12.10.2017

Accepted: 02.20.2018

### ÖZET

**Amaç:** Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) tanısı alan ve metilfenidat tedavisi başlanan hastalarda nadiren kardiyovasküler yan etkilerin görülebildiği bilinmektedir. Bu çalışmada merkezimizde metilfenidat tedavisi başlanan DEHB'li hastaların tedavi öncesi ve sonrası kardiyak değerlendirmesi amaçlanmıştır.

**Yöntem:** DEHB tanısı ile metilfenidat başlanan 253 hastanın verileri retrospektif olarak tedavi öncesi ve iki hafta sonrasında değerlendirildi. Hastaların demografik verileri, kalp hızı, sistolik ve diastolik kan basıncı, elektrokardiyografi (EKG) ile düzeltilmiş QT (QTc) süresi ve ekokardiyografik incelemeleri tedavi öncesi ve sonrası karşılaştırıldı.

**Bulgular:** Yaş ortalaması  $11,8 \pm 3,3$  yıl olan hastaların 18 (%7) tanesinde ilaç sonrası çarpıntı ve 5 (%1,9) tanesinde tansiyon yüksekliği bulguları izlendi. Çarpıntısı olan hastaların hepsinde sinüzal taşikardi izlenirken, tansiyon yüksekliği saptanan beş hastanın tedavileri sonlandırıldı. Ekokardiyografide dört hastada sekondum atrial septal defekt, iki hastada valvüler pulmoner stenoz, bir hastada ventriküler septal defekt ve bir hastada patent duktus arteriozus saptandı. Hastaların tedavi sonrası kalp hızı, sistolik ve diastolik tansiyon değerlerinde ilaç öncesine göre istatistiksel olarak anlamlı bir fark görülmedi. Tedavi sonrası QTc sürelerinin anlamlı olarak uzadığı görülse de bu değerlerin patolojik seviyeyi aşmadığı görüldü.

**Sonuç:** DEHB'li çocukların metilfenidat tedavisi sonrası değerlendirmeleri hastaların ek özelliklerine göre değişmelidir. DEHB nedeniyle metilfenidat kullanımı öncesi yapısal kalp hastalığı olan veya arteriyal hipertansiyonu eşlik eden hastalar daha dikkatli izlenmelidir. Çalışmamız hem kan basıncı ölçümü hem de elektrokardiyografi değerlendirmesinin metilfenidat tedavisinden sonra yan etkileri saptamak için yararlı ve uygun yöntemler olduğunu belirtmektedir.

**Anahtar Sözcükler:** Dikkat eksikliği hiperaktivite bozukluğu, metilfenidat, yapısal kalp hastalığı, elektrokardiyografi, hipertansiyon, aritmi

Geliş Tarihi: 10.12.2017

Kabul Tarihi: 20.02.2018

ORCID IDs: E.C. 0000-0001-8485-0376, E.Y. 0000-0001-5435-6342, A.E. 0000-0002-7553-5013

Address for Correspondence / Yazışma Adresi: Erman Cilsal, MD Serinevler Mah. Ege Bagtur Cad. Yuregir, Adana, Turkey E-mail: ermancilsal@gmail.com

©Telif Hakkı 2020 Gazi Üniversitesi Tıp Fakültesi - Makale metnine <http://medicaljournal.gazi.edu.tr/> web adresinden ulaşılabilir.

©Copyright 2020 by Gazi University Medical Faculty - Available on-line at web site <http://medicaljournal.gazi.edu.tr/>

doi:<http://dx.doi.org/10.12996/gmj.2020.84>

**INTRODUCTION**

Attention deficit and hyperactivity disorder (ADHD) is the most common of all neurodevelopmental disorders and is seen in children of school age at the rates ranging from 8 to 11% (1, 2). Hyperactivity and impulsivity constitute ADHD symptoms in two main topics. These symptoms typically begin at around the age of 4 years and reach a peak at 7–8 years old. At this age, symptoms of hyperactivity begin to decrease and may reach an imperceptible level in the adolescence period, while in contrast, impulsive symptoms may persist throughout life. Diagnostic criteria for ADHD were published in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders, Edited by the American Psychiatric Association with consensus (3). ADHD may cause a person to behave in a way that is not appropriate for his or her age and is characterized by a decreased ability to focus attention or hyperactivity/impulsivity. Behavioral and emotional disorders may accompany in approximately 50% of cases, and these disorders may occur primarily or secondarily with the exacerbation of ADHD. Pharmacological treatment is recommended for the patients who do not respond to behavioral approaches (4). Stimulant agents are recommended as the first choice when the clinician and the family decide to start medication (5), as their effects can be noted in a shorter time and they are effective and safe for long-term use (6). Available stimulants include methylphenidate (Ritalin, Concerta, Medikinet), dextroamphetamine (Dexedrine) and mixed amphetamine salts (Adderall), all of which have been used effectively in treatment. Unexpected sudden deaths have been reported in children who have undergone such treatments, and this has led to concerns that the medication may lead to increased cardiovascular risk (7), although in large community-based cohort studies, no statistically significant difference was reported in the presence of severe cardiovascular events (sudden death, acute myocardial infarction, stroke) among children who were receiving no medication at the time and those with no medication history, and those who were being treated with medication at the time (8,9). Incidences of neurodevelopmental disorders, such as ADHD are higher in children with congenital heart disease, as one of the most common congenital defects. There have been reports stating that more attention should be paid to the side effects of the stimulant agents used in the treatment of these patients in the next period (10). Treatment doses of stimulants are known to increase the heart rate, systolic and diastolic blood pressure, and the potential for QTc prolongation, arrhythmia and sudden death has also been reported (11).

In this study, we evaluate the changes in the cardiovascular parameters in the early post-treatment period of children with ADHD who have begun methylphenidate treatment.

**MATERIALS and METHODS**

Our single-center, cross-sectional study involved examining retrospectively the medical records of patients diagnosed with ADHD who were referred to the hospital before treatment. Ethics Committee Approval of Adana City Hospital was obtained for this study. Data on 258 patients diagnosed with ADHD who were referred to the Adana Numune Education and Research Hospital Pediatric Cardiology Clinic between August 2016 and August 2017 before beginning treatment was examined, and 253 patients were included in our study. Only those patients who had used the methylphenidate agent in the form of a controlled release tablet were included in this study. Data from before the onset of methylphenidate treatment and in the second week of treatment were obtained from the records. For the post-medication control, the patients were evaluated in the morning, two hours after receiving medication as in pre-medication control. The initial dose of methylphenidate treatment was observed to be 0.5-0.75 mg/kg/day. The pre- and post-medication blood pressure measurements of the patients were carried out using a cuff and mercury sphygmomanometer (ERKA perfect aneroid) that was suitable for right upper arm measurements in a sitting position after five minutes rest. The mean blood pressure measurements were calculated manually (systolic blood pressure + pulse pressure)/3, while the demographic characteristics were recorded, and the heart rates, systolic and diastolic blood pressures of the patients, as well as the QTc duration, were determined through electrocardiography (ECG). Accompanying structural heart diseases were investigated via an ECG and pre- and post-medication values were compared. Heart rate was calculated during the evaluation of vital signs rather than from the ECG records.

Patients on medication other than methylphenidate, patients using additional antipsychotic medication, and patients with additional systemic disease, such as systemic hypertension or diabetes mellitus, were excluded from this study.

*Statistical Analysis*

Paired Sample T-Test was used after it was ascertained that the distribution of data before and after methylphenidate was normal. A *p*-value of <0.05 was considered statistically significant. The statistical analysis was carried out using SPSS version 25.0 software (IBM Corporation, Armonk, NY, USA).

**RESULTS**

Of the total 253 patients included in this study, 54% were male and 46% were female. The demographic data of the patients included in the study are presented in Table 1. The mean age of the patients was 11.8±3.3 years. Of the 253 patients who were evaluated before treatment, 18 (7.1%) were observed to have palpitation complaints after medication, and sinus tachycardia was observed in all of these, while medication was discontinued in the five of these patients since their blood pressures were at the peak level when compared to the patients' sex and height percentage. Two patients were diagnosed with essential hypertension, and one was diagnosed with white coat hypertension due to the high blood pressure levels.

**Table 1.** Demographic data of the study group

	Patient (n: 253)
Age (years)	11.8 ± 3.3
Sex (F/M)	137/116
Weight (kg)	39.6 ± 8.4
Height (cm)	145.6 ± 7.4

Data were expressed as mean value ± SD.

In the pre-treatment ECG examinations of the patients carried out to determine the presence of any structural heart disease, 23 patients (9%) were observed to have heart disease. Data on the congenital and acquired heart diseases identified in the patients is presented in Table 2. Patent foramen ovale (PFO) was identified in four patients, and four patients were determined to have secundum atrial septal defects (ASD). Operations were scheduled for two patients after the identification of large ASDs, and no medical treatment was initiated. Mitral insufficiency (MI), thought to be related to previous rheumatic heart disease, was observed in three patients and aortic insufficiency (AI) was observed in two patients. In addition, two patients were observed to have mild pulmonary valve stenosis (PVS), one patient had a small ventricular septal defect (VSD), and one patient had a fine patent ductus arteriosus (PDA).

**Table 2.** Transthoracic echocardiogram findings before the methylphenidate treatment

	n	%
PFO	4	1.58
Secundum ASD	4	1.58
Mitral insufficiency	3	1.18
BAV	3	1.18
Aortic insufficiency	2	0.79
PS valvular	2	0.79
VSD	1	0.39
PDA	1	0.39
Normal heart findings	233	92
TOTAL	253	100

ASD: Atrial septal defect, AI: Aortic insufficiency, BAV: Bicuspid aortic valve, MI: Mitral insufficiency, PDA: Patent ductus arteriosus, PFO: Patent foramen ovale, PS: Pulmonary stenosis, VSD: Ventricular septal defect.

The pretreatment systolic blood pressures of the patients included in this study were  $103.9 \pm 9.9$  mmHg, diastolic blood pressure was  $66.1 \pm 8.1$  mmHg and mean blood pressure values were  $79.1 \pm 9.2$  mmHg. Post-treatment values were found to be  $103.3 \pm 11.4$  mmHg,  $65.8 \pm 8.2$  mmHg and  $78.6 \pm 9.7$  mmHg, respectively. No statistically significant difference was observed in the systolic, diastolic and mean blood pressures of the patients before and after medication ( $p=0.167$ ,  $p=0.272$ ,  $p=0.189$ ) (Table 3). The pretreatment heart rates of the patients were  $83.9 \pm 13.1$ /min, compared to  $84.3 \pm 13.2$ /min after treatment. There was no statistically significant difference in either group regarding heart rates before and after the treatment ( $p=0.154$ ) (Table 3).

**Table 3.** Data before and after methylphenidate treatment

	Pre-medication	Post-medication	
EF	$70.2 \pm 4.6$		
FK (%)	$38.9 \pm 4.6$		
LVIDd (mm)	$38.4 \pm 5.1$		
Heart rate (min)	$83.9 \pm 13.1$	$84.3 \pm 13.2$	0.154
QTc (msec)	$0.37 \pm 0.51$	$0.41 \pm 0.34$	0.003*
BP systolic (mmHg)	$103 \pm 9.9$	$103.3 \pm 11.4$	0.167
BP diastolic (mmHg)	$66.1 \pm 8.1$	$65.8 \pm 8.2$	0.272
BP mean (mmHg)	$79.1 \pm 9.2$	$78.6 \pm 9.7$	0.189

Data expressed as mean value  $\pm$  SD.

Paired t-test  $p < 0.05$  was considered statistically significant.

BP: Blood pressure, EF: Ejection fraction, FK: Fractional shortening, LVIDd: Left ventricular internal diastolic diameter.

The pretreatment QTc duration of the patients, calculated from their ECG, was  $0.37 \pm 0.51$  msec, and was observed to be  $0.41 \pm 0.34$  msec after treatment. When a comparison was made of the patient's QTc durations before and after the medication, an increase was noted after treatment that was found to be statistically significant ( $p=0.003$ ). None of these values were found to be at pathological levels after medication (Table 3).

## DISCUSSION

There are conflicting opinions regarding the safe use of stimulated and non-stimulated drugs in the treatment of ADHD regarding their potential to cause cardiovascular disease. Methylphenidate, which is commonly used in the treatment of ADHD as a stimulant, is in frequent use in our country and around the world. Methylphenidate treatment has been reported to increase heart rate, systolic and diastolic blood pressure, and to cause QTc prolongation. Although methylphenidate has been reported to be safe in large series of studies of adult patients, the power analysis is limited due to the limited number of studies that involve children. In a study by Mick et al. (11) including a large series, the use of stimulant drugs was shown statistically to increase heart rate. The increase of 1-4 mmHg in systolic blood pressure, 1-2 mmHg increase in diastolic blood pressure and around 1-2 pulse/min increase in heart rate specified in a report of the ADHD Guidelines Group were not observed in our study (12). In our study, no significant change was observed in the post-medication heart rate levels in the early period. Drug levels obtained during the titration period at the beginning of treatment have been thought to play a role in the change in blood pressure and heart rate effects (13). In our study, patients were evaluated during post-treatment second week control, in which no dose titration was performed, and for this reason, no statistically significant increase was observed in blood pressures and heart rates. In a prospective study by Kim et al. (14) in which heart rate variability was evaluated for treatment response, parasympathetic system dominance was observed in children with ADHD before medication when compared to the control group, and it was seen to decrease after treatment with methylphenidate. It was thus concluded that the drug played a role in the efficacy of treatment by providing autonomic balance in addition to its simple effects, and for this reason, it has been reported to be safe and is not associated with severe cardiovascular diseases, although it may increase the heart rate with long-term use. In a study carried out in children to evaluate acute effects at the second hour after methylphenidate treatment, no significant difference was observed in QT, QTc and QT dispersion duration in ECG (15).

In large-scale studies, no change was observed in diastolic pressures, whereas systolic blood pressure values were reported to be significantly higher in adolescents using methylphenidate at 1.5 mg/kg, prospectively (13). Concerning the dose, in our study, no significant changes were observed in the vital signs of the patients in their early period evaluations after the initial doses. In a study of 1,244 children under the age of 17, Shin et al. (16) found that the risk of arrhythmia was higher between one and three days after starting medication, although this risk decreased as the duration of treatment was prolonged (>56 days). In the same study, the risk of arrhythmia was found to be higher after methylphenidate use in patients with congenital heart disease than in those without, although no difference was observed in hypertension development risk. In our study, no medical treatment was initiated, since it was decided to schedule two patients for operations due to ASD in the evaluation for congenital heart disease before treatment. Treatment was started for other patients with congenital and acquired heart diseases when no hemodynamic changes, and no posttreatment dysrhythmia and hypertension, were observed.

Sudden cardiac death associated with stimulants is known to be linked to *torsades de pointes*, which is polymorphic ventricular tachycardia with a long QT interval (17). Hence, a QTc duration of >500 msec, which is corrected for heart rate in clinical practice, is used as a predictor of fatal arrhythmias. Although no change was reported in QTc duration after methylphenidate treatment in previous studies, it was observed to be prolonged significantly in our study, which is in parallel with several studies in the literature. However, we should note that none of the studies reached a pathological level. In a small number of reliability studies that involved children before the methylphenidate treatment and after its long-term use, no significant changes in cardiovascular parameters were identified (18).

In conclusion, no serious cardiac effects were observed following the use of methylphenidate in our study, although patients should be evaluated for structural heart disease before the treatment. Patients should be followed closely during long-term medication use. However, it is notable that the increases in blood pressure values and QTc duration were not statistically significant, and were within normal limits.

## Conflict of interest

No conflict of interest was declared by the authors.

## REFERENCES

- Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. *Pediatrics* 2010;125: 75-81
- Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, Ghandour RM, Perou R, Blumberg SJ. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *Journal of the American Academy of Child and Adolescent Psychiatry* 2014;53: 34-46 e32
- Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. *Indian J Psychiatry* 2013;55: 220-3
- Subcommittee on Attention-Deficit/Hyperactivity D, Steering Committee on Quality I, Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011;128: 1007-22
- Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M, Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity D. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2006;45: 642-657
- Storebo OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, Rosendal S, Groth C, Magnusson FL, Moreira-Maia CR, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbol B, Simonsen E, Gluud C. (2015) Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *The Cochrane database of systematic reviews*: CD009885

7. Nissen SE. ADHD drugs and cardiovascular risk. *The New England journal of medicine* 2006;354: 1445-8
8. Winterstein AG, Gerhard T, Kubilis P, Saidi A, Linden S, Crystal S, Zito J, Shuster JJ, Olfson M. Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study. *Bmj* 2012;345: e4627
9. Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, Daniel GW, Cziraky MJ, Hennessy S. Cardiovascular events and death in children exposed and unexposed to ADHD agents. *Pediatrics* 2011;127: 1102-10
10. Batra AS, Alexander ME, Silka MJ. Attention-deficit/hyperactivity disorder, stimulant therapy, and the patient with congenital heart disease: evidence and reason. *Pediatr Cardiol* 2012;33: 394-401
11. Mick E, McManus DD, Goldberg RJ. Meta-analysis of increased heart rate and blood pressure associated with CNS stimulant treatment of ADHD in adults. *Eur Neuropsychopharmacol* 2013;23: 534-41
12. Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Graham J, Taylor E, Sergeant J, European AGG. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry* 2013;54: 227-46
13. Hammerness P, Wilens T, Mick E, Spencer T, Doyle R, McCreary M, Becker J, Biederman J. Cardiovascular effects of longer-term, high-dose OROS methylphenidate in adolescents with attention deficit hyperactivity disorder. *J Pediatr* 2009; 155: 84-89, 89 e81
14. Kim HJ, Yang J, Lee MS. Changes of Heart Rate Variability during Methylphenidate Treatment in Attention-Deficit Hyperactivity Disorder Children: A 12-Week Prospective Study. *Yonsei Med J* 2015;56: 1365-71
15. Lamberti M, Italiano D, Guerriero L, D'Amico G, Siracusano R, Ingrassia M, Germano E, Calabro MP, Spina E, Gagliano A. Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder. *Neuropsychiatr Dis Treat* 2015;11: 1169-74
16. Shin JY, Roughead EE, Park BJ, Pratt NL. Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. *Bmj* 2016;353: i2550
17. Berg A, Bratane E, Odland HH, Brudvik C, Rosland B, Hirth A. Cardiovascular risk assessment for the use of ADHD drugs in children. *Tidsskr Nor Laegeforen* 2014;134: 710-4
18. Arcieri R, Germinario EA, Bonati M, Masi G, Zuddas A, Vella S, Chiarotti F, Panei P, Italian Attention-Deficit/Hyperactivity Disorder Regional Reference C. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *Journal of child and adolescent psychopharmacology* 2012;22: 423-31