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Cardiovascular effects of methylphenidate in children with attention deficit hyperactivity disorder (ADHD)

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Abstract
The present study was conceived with the objective to examine the effects of methylphenidate on cardiovascular variables in children with Attention-deficit/hyperactivity disorder (ADHD). ECG indices plus systolic blood pressure (SBP), diastolic BP (DBP) and heart rate (HR) were assessed in 52 children with ADHD (dosage of 0.3- 1 mg/ kg body weight). Cardiovascular parameters were assessed at baseline and 12 weeks. Small but statistically significant changes in DBP and HR were observed at 12 weeks without clinically meaningful changes in ECG. Increase in heart rate and Blood pressure could be attributed to the increased sympathetic activity caused by methylphenidate.
Keywords: *methylphenidate, ADHD, Cardiovascular effects.*

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children and adolescents with the estimated worldwide prevalence of 7.2 %[2]. Attention-deficit/ hyperactivity disorder (ADHD) is characterized by a pattern of decreased sustained attention and a higher level of impulsivity in a child or adolescent than is expected for someone of that age and developmental level[1]. Psychostimulants like methylphenidate that increase dopamine concentrations and the selective noradrenaline transporter inhibitor atomoxetine which increases noradrenaline levels have been used in the treatment of ADHD by targeting the central nervous system[3].

Methylphenidate is used as the first-line drug for treatment of children and adolescents with ADHD[4]. The present study was planned with the objective of studying the changes in heart rate and blood pressure before and after methylphenidate treatment in drug-naive patients with ADHD.

Aim

To examine the effects of methylphenidate on cardiovascular variables in children with attention deficit hyperactivity disorder (ADHD).

Methods

The present study was carried out in the Department of Physiology in association with the Department of Psychiatry at Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital, New Delhi. The study was approved by the institutional ethics committee for human research of Lady Hardinge Medical College, New Delhi.

The study was carried out on 52drug naïve males, 6-12 years of age diagnosed to be suffering from ADHD by an experienced psychiatrist as per the fifth edition of the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-V)[5]. The wards of consenting parents for the study were recruited as per inclusion and exclusion criteria from Psychiatry OPD of Lady Hardinge Medical College & Smt. S. K. Hospital, New Delhi. No female patient was included in the study group as they did not meet our inclusion criteria. The mean age of these patients was 8.21 ± 0.14 yrs. Known patients with hepatic, renal, cardiovascular diseases, diabetes mellitus systemic inflammatory disorders were excluded from the study. Patients showing other psychiatric co-morbidities including autism, oppositional defiant disorder, and conduct disorder were also excluded from the study. A parent or legal guardian of the patients provided the informed written consent which was written in either Hindi or English.

The subjects were called to the Department of Physiology in morning hours. They were instructed to abstain from tea/coffee/nicotine for at least 2 hours before the recording. No psychotropic medications were permitted to the subjects before the start of the study. A detailed history was taken,and general physical examination was carried out. All data were recorded in the Performa. All the tests were performed in a quiet and isolated room, and the ambient temperature maintained at 23-25°C. The subjects were allowed to adapt to the experimental conditions and ample time was given to relax. All patients were examined and tests performed on them in the presence of parent(s) / guardian. Baseline H.R., B.P.,and ECG were recorded. The ECG was recorded using BPL CARDIART 6208 ECG machine. Blood pressure was measured by auscultation using a standard aneroid sphygmomanometer with B.P. cuff of suitable size, in sitting position, after 10 minutes of rest from the right arm. As per the guidelines of American Heart Association, three blood pressure readings were taken at five minutes intervals and systolic, and diastolic blood pressure was calculated by averaging the last two readings.

The patients were then put on methylphenidate in a dosage of 0.3- 1 mg/ kg body weight either immediate or extended release medications for a period of 12 weeks. The mean dose at the endpoint of the study was 20.58±3.52 mg equivalent to a dose of 0.70 ± 0.09mg per kg of body weight.

All the above parameters were repeated at 12 weeks of study period.

Data obtained was subject to statistical evaluation using a Graph Pad Prism Version 7 software. The D'Agostino & Pearson normality test, Shapiro-Wilk normality test and KS normality test were applied to test for normal Gaussian distribution. The mean and standard error of mean (Mean ± SEM) of all variables for both groups were calculated according to accepted statistical methods. Wilcoxon matched-pairs signed rank test was used to compare the difference from baseline to 12 weeks after methylphenidate treatment.

Results

No significant changes in weight and BMI were observed from baseline to 12 weeks of study (Table

1). There was a significant increase in the heart rate from baseline to 12 weeks of methylphenidate treatment. The mean value of Systolic Blood Pressure did not vary significantly from baseline to after treatment. However, there was a significant increase in Diastolic Blood Pressure after 12 weeks of methylphenidate treatment (Table 2). No clinically meaningful changes were observed in ECG from baseline to 12 weeks of methylphenidate treatment.

No serious adverse events were reported during the study period.

Table 1: Changes in weight and BMI from baseline to 12 weeks after methylphenidate treatment(Mean ± S.E.M values)

Parameters	Baseline	After treatment	P value
Weight(kg)	**29.44±0.45**	**29.43±0.45**	**0.9970**
BMI(kg/m^2)	**16.38±0.23**	**16.33±0.22**	**0.2732**

p value- > 0.05-Non-Significant (NS),<0.05-Significant*, <0.01-Very Significant**, <0.001-Highly Significant***

Table 2: Changes in resting heart rate(HR), Systolic blood pressure(SBP) and Diastolic Blood Pressure(DBP) from baseline to 12 weeks after methylphenidate treatment in the study group (Mean ± S.E.M values)

Parameters	Baseline	After treatment	P value
HR(beats/min)	87.08± 1.78	98.38 ± 3.21	0.0001
SBP(mm Hg)	104.30± 0.45	104.8 ± 0.49	0.1805
DBP(mm Hg)	67.46 ± 0.50	68.15 ± 0.43	0.0001

p-value- > 0.05-Non-Significant (NS),<0.05-Significant*, <0.01-Very Significant**, <0.001-Highly Significant***

Discussion

Our study is in concordance with the study by Bange et al. 2014[6]. The authors have reported an increase in Heart Rate and Blood pressure after treatment with Methylphenidate in children with ADHD. They have however found no increase in Myocardial infarction, stroke, and sudden cardiac deaths. Amanet al. in 1975also reported a small trend toward an increment in heart rate and a significant increment in blood pressure[7]. However, Garg et al. found only a significant increase in heart rate[8]. Further Romano Arcieriet al. 2016 reported an association with increased risk of arrhythmia and Myocardial infarction but found no increased risk of hypertension, stroke and heart failure[9].

The fact that methylphenidate was associated with an increase in heart rate and Blood pressure could be attributed to the adrenergic effects wherein methylphenidate increases sympathetic activity.

Increase in heart rate and DBP warrants a cautious use of Methylphenidate more so in children with cardiac diseases.

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