

## Original Article

## Does 20 mg long-acting methylphenidate alter blood pressure and heart rate in children with ADHD?

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### Abstract

**Objective** To identify the cardiovascular effects of long-acting methylphenidate administered for twelve weeks in Indonesian children with ADHD.

**Methods** This was an 18-week, time series study on children with ADHD who were given 20 mg of long-acting methylphenidate for twelve weeks. During the study period we made ten serial observations of the subjects, including before, during and 6 weeks following drug administration. We included drug naive children with ADHD between the ages of 7 – 10 years. Children with mental retardation and chronic physical or mental disorders were excluded. Blood pressure was measured by sphygmomanometer with a child's cuff at the brachial artery. We also collected data on heart rate, side effects, complaints and other medications used during the study. Repeated analysis was performed on the data with a P level of 0.05.

**Results** Twenty-one subjects were recruited for this study. Mean blood pressure fluctuated insignificantly during the research period, for both mean systolic and mean diastolic blood pressures ( $P=0.115$  and  $P=0.059$ ). Mean heart rate also fluctuated insignificantly ( $P=0.091$ ). All fluctuations were within the normal ranges. During the study, there were complaints of dizziness, nausea, and gastrointestinal upset, but they were reportedly mild and disappeared before the second week of observation.

**Conclusion** Administration of 20 mg long-acting methylphenidate for twelve weeks in children with ADHD altered mean blood pressures and heart rates, but within the normal range for children of their age. However, cardiovascular risk observation is still needed when administering methylphenidate to children with ADHD, especially for those using the medication long-term. [Paediatr Indones. 2011;51:282-7].

**Keywords:** ADHD, children, long-acting methylphenidate, blood pressure, heart rate

Methylphenidate hydrochloride is a mild, central nervous system psychostimulant belonging to the sympathomimetic amine drug family. It is used mainly to treat children with Attention Deficit and Hyperactivity Disorder (ADHD) and sometimes for narcolepsy. Methylphenidate hydrochloride effectiveness in treating ADHD has been documented in many studies, along with its safety profiles.<sup>1-5</sup>

Many clinical trials have shown that methylphenidate improves the clinical symptoms of ADHD, including hyperactive and impulsive behavior, attention span, working memory, and executive function. It also increases quality of life in general.<sup>6-9</sup>

Methylphenidate works by binding the dopamine transporter (DAT-1) in pre-synapse neurons, thus decreasing reuptake of dopamine neurotransmitters and enhancing dopaminergic neurotransmission, especially in the prefrontal cortex. In addition,

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it has been reported that methylphenidate also influences the serotonergic and noradrenergic neurotransmission.<sup>10-16</sup>

Volkow *et al.* reported that giving 20 mg of long-acting methylphenidate orally to children with ADHD increased the dopamine neurotransmitter in the dorsal striatum cortex.<sup>15</sup> Marsteller *et al.* also reported similar effects in mice, and assumed that giving 20 mg of methylphenidate would decrease 50% of DAT-1 function in the prefrontal cortex.<sup>17</sup>

Methylphenidate is available in immediate-release, slow-release, and long-acting forms. Efficacy is 75–80% in these three regimens, and not significantly different, except in pharmacodynamic profiles on behavior and performance in class settings. However, long-acting methylphenidate is preferred since it is given only once daily.<sup>8,18,19</sup>

In spite of the efficacy in reducing ADHD symptoms, there is controversy in prolonged therapy and its side effects.<sup>2,4,5,20,21</sup> The most common side effects are low appetite, nervousness, sleep difficulties, tachycardia, and increased blood pressure. The cardiovascular safety of methylphenidate has been a major concern of many physicians and parents.<sup>4,5,18,22,23</sup> A study in acquired brain injury patients showed that there was no statistically significant effect of short-acting methylphenidate on blood pressure.<sup>19</sup> Other studies have shown that children and adults with ADHD taking methylphenidate have minor mean increased blood pressure and heart rate compared to baseline measurements.<sup>23,24</sup>

For this reason, we sought to review the effect of a 12 week-administration of 20 mg long-acting methylphenidate on blood pressure and heart rate in Indonesian children with ADHD. We also identified side effects of methylphenidate in our subjects.

## Methods

We used a time series design for this study, as our main purpose was to identify mean differences of blood pressure, heart rate, as well as body weight and height before, during (for 12 weeks), and after (for 4 weeks) administering 20 mg long-acting methylphenidate.

We made ten serial observations during the 18-week period of study, each observation for two weeks. Observations were divided into (1) baseline, the first

observation before subjects took methylphenidate; (2) the 2<sup>nd</sup> – 7<sup>th</sup> observations, the periods in which subjects took 20 mg long-acting methylphenidate; (3) the 8<sup>th</sup> observation, the period in which the methylphenidate dose was tapering off; and (4) the 9<sup>th</sup> – 10<sup>th</sup> observations, after methylphenidate was discontinued. Observations were performed 6 hours after administering the 20 mg long-acting methylphenidate (during which the methylphenidate hydrochloride plasma level reaches its second peak).

Subjects were children with ADHD treated at the Child and Adolescent Psychiatry Outpatient Clinic in Cipto Mangunkusumo General Hospital and the Developmental Clinic at Pantai Indah Kapuk Hospital, Jakarta. Subjects were between 7–10 years in age. ADHD was diagnosed by MINI with children's guidelines, translated into the Indonesian language.<sup>25</sup> All subjects were drug naïve and had no physical or mental chronic illnesses, except for ADHD. Children with mental retardation were also excluded. Subjects who completed less than 80% of the study were not included in the analysis. Consecutive sampling was used to recruit subjects from January–July 2008. We used sample size tables for clinical studies to determine the sample size.<sup>26</sup> All parents gave written informed consent. The study protocol was approved by the Faculty of Medicine Ethics Committee, University of Indonesia.

Subjects' blood pressures were measured by sphygmomanometer using a children's cuff at the right upper arm. The cuff was placed on the inside of the elbow, above the brachial artery. Blood pressure was expressed as systolic and diastolic pressures (mmHg). Heart rate was counted manually by listening to the heart beat with a stethoscope on the subject's chest for one minute duration (beats per minute/bpm). At every observation session, we also recorded participants' body weights and heights, noted any health-related complaints and the use of medications other than that provided in the study.

ADHD clinical symptoms were monitored by using the *Skala Penilaian Perilaku Anak Hiperaktif Indonesia* questionnaire (SPPAHI, the Indonesian Hyperactive Behavior Assessment Scale for Children), which was completed by subjects' parents every two weeks. The SPPAHI consists of a 35-item scale that measures hyperactive-impulsive and inattentive symptoms in children aged 6 to 13 years. Each item,

in turn, is answered on a 4-point scale, ranging from “never happens” (0) to “always observe” (3). Scores are calculated by summing these responses across the 35 items. The sensitivity and specificity of this scale are 0.613 and 0.768, respectively.<sup>27</sup> A Clinical Global Impression of Severity scale (CGI-S) was also assessed during each observation by the researcher.

Repeated measure test was used to analyze the difference in mean blood pressure (both systolic and diastolic), heart rate, and body weight and height. We used a P value < 0.05, as the criterion of statistical significance. All data was analyzed by SPSS 16.0 for graduate students.

## Results

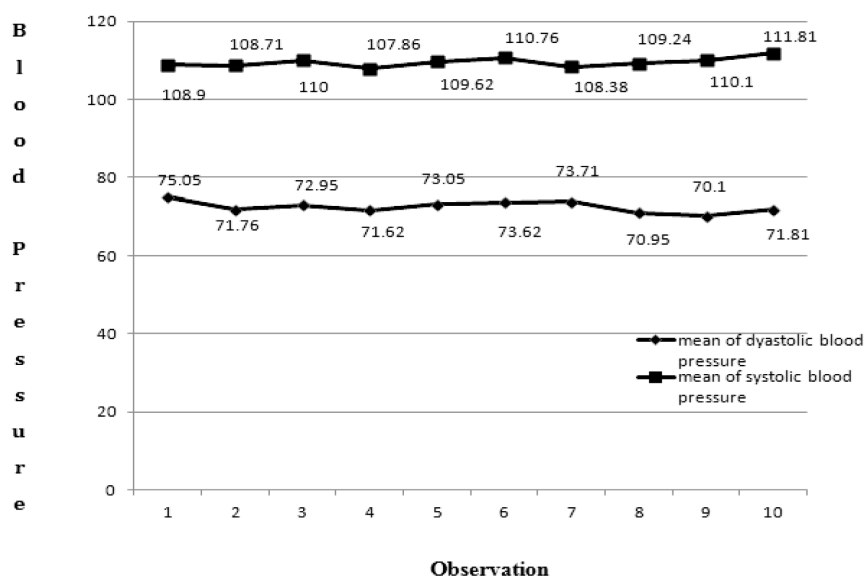
Twenty-one subjects fully complied with the study protocol during the study period. ADHD subjects had either the combined type (15 subjects) or the inattentive type (6 subjects). There were more male subjects than females (ratio of 4:1). The average age was 8.52 years (SD 1.08) with the 95% confidence interval ranging from 8.03 to 9.01. Their intellectual level was within normal range at 110.14 (SD 16.578) with the 95% confidence interval ranging from 102.60 to 117.69. Most subjects’ academic achievements were within the class average (12 subjects), with 6 below and 3 above the class average. (Table 1)

Eighteen subjects were reported to have been delivered normally without complications, while two subjects were delivered by Caesarean section due to placenta previa and post-maturity, and one subject was delivered by vacuum extraction. There was no history of neonatal asphyxia or other perinatal illnesses in any of the subjects. Developmental histories were also normal.

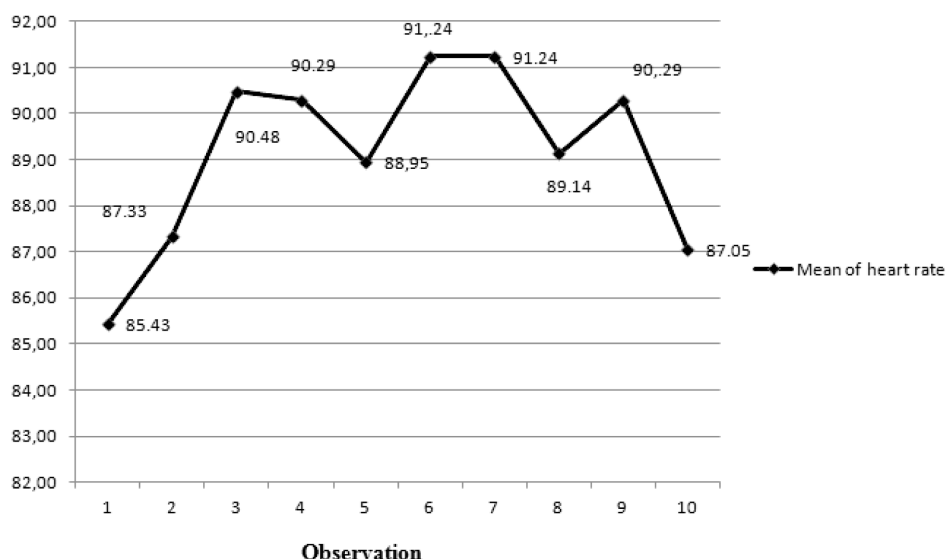
The mean baseline systolic and diastolic blood pressures were 108.90 (SD 8.83) mmHg and 75.05 (SD 7.66) mmHg, respectively. The mean blood pressure of subjects at each observation did not fluctuate significantly for either systolic or diastolic blood pressures (P=0.115 and P=0.059, respectively)

**Table 1.** Characteristics of research subjects

Characteristic	Mean (SD)	Frequency
Age (year)	8.52 (1.08)	
Gender		
Boy		17
Girl		4
Academic achievement		
Under-class average		6
Average		12
Above- class average		3
ADHD type		
Combined type		15
Inattentive type		6
Total IQ	110.14 (16.58)	
Verbal IQ	107.57 (17.50)	
Performance IQ	110.10 (14.33)	



**Figure 1.** Repeated measures mean systolic and diastolic blood pressure (mmHg) during the eighteen week observation (n=21, p=0.115 and p=0.059)



**Figure 2.** Repeated measures mean heart rate (beats per minute) during the eighteen week observation (n=21, p=0.191)

during and after methylphenidate administration as shown in **Figure 1**.

The mean baseline heart rate was 85.43 (SD 7.70) bpm. It also did not fluctuate significantly, before, during or after methylphenidate administration (P=0.091), as shown in **Figure 2**.

Mean SPPAHI score decreased significantly, especially in the first two weeks of observation, and increased slightly after methylphenidate was discontinued, but remained below the baseline mean (P=0.001). (**Table 2**) Mean baseline body weight and height were 36.20 (11.88) kg and 132.40 (9.55) cm. During the eighteen week observation, the mean body weight decreased during the first ten week observation period and then increased until the end of the research period (P=0.005). In the meantime, the mean height increased by 0.87 cm during the research period (P=0.001).

During the research period, 5 subjects were diagnosed with upper respiratory infections. The symptoms were coryza, cough, sore throat, and excessive nasal secretions, which were relieved within 4 – 7 days. The medications used to reduce the symptoms were paracetamol, ambroxol hydrochloride, pseudoephedrine HCl, terfenadine, and azithromycin. Methylphenidate was given as usual.

In the first week of administering methyl-

phenidate, 4 subjects complained of dizziness, nausea, and gastrointestinal discomfort. These complaints were categorized as mild and did not last more than one week. There was no specific action taken to minimize these side effects.

By clinical examination with CGI-S, 5 children (24%) were categorized with severe ADHD, while the remaining was categorized with moderate ADHD. After administering methylphenidate for 12 weeks, the degree of severity decreased significantly, with 95% of subjects categorized in the normal range. Subjects continued to be categorized in the normal range, even after medication was discontinued for a month.

**Table 2.** Repeated measures of mean SPAHHI score, mean body weight (kg), and mean body height (cm) during eighteen weeks observation (n= 21, P<0.05)

Observation Week	Mean SPAHHI	Mean body weight, kg	Mean body height, cm
0	53.86	36.20	132.40
2	22.33	35.74	132.50
4	18.71	35.46	132.60
6	13.29	35.92	132.60
8	13.33	35.45	132.68
10	12.14	35.32	132.79
12	11.00	35.79	132.95
14	14.90	36.00	133.08
16	22.00	36.17	133.16
18	24.52	36.47	133.27

## Discussion

Long-acting methylphenidate has been widely used in treating children and adolescents with ADHD, although the number of randomized clinical trials on this medication is limited. Several long-term studies indicate that a multimodal treatment is the best approach in helping children with ADHD. Our results showed that administering 20 mg of long-acting methylphenidate for twelve weeks reduced ADHD symptoms. The efficacy remained good even after the medication had been discontinued for four weeks. Subjects showed better outcomes in academic achievements and social interactions. This finding is similar to other previous studies on the effects of long-acting methylphenidate in children with ADHD.<sup>1,4,8</sup>

An open-label trial of once daily, osmotic-release methylphenidate in 432 children (aged 6 to 13 years) with ADHD for 12 months resulted in a minor, but statistically significant increase in mean blood pressure and heart rate.<sup>23</sup> Similar effects were also observed in an adult ADHD study.<sup>22</sup> However, a study in patients with acquired brain injuries showed that long-acting methylphenidate did not increase blood pressure and heart rate.<sup>19</sup> We found that in children with ADHD, administering 20 mg of long-acting methylphenidate for 12 weeks induced fluctuations in mean blood pressures and heart rate, but they were statistically insignificant compared to those of baseline, and also to those at 4 weeks after discontinuation of the medication.

We observed the normal alteration of mean systolic and diastolic blood pressures, as well as heart rates during the research period. Our subjects had no clinical, cardiovascular complaints during the research period, such as palpitations. But precautions should still be taken, especially for patients with known risk factors such as coronary artery disease, structural cardiac abnormalities, pre-existing cardiovascular diseases, and hypertension.

The frequent adverse reactions in our subjects were mild symptoms of dizziness, nausea, and gastrointestinal discomfort. Previous studies have also shown similar side effects, but our subjects' complaints were of short duration and did not impact their daily routines.

Decreased body weight and height is a concern for children with ADHD who take methylphenidate. A longitudinal study of children with ADHD aged 7 – 10 years, showed a temporary growth decrease after

3 years of continuous methylphenidate. Their mean body weight was 2.7 kg and mean height was 2 cm lower compared to normal children.<sup>14</sup> We observed that mean body weight decreased in the first six weeks of methylphenidate administration, followed by a growth rebound starting in the twelfth-week of observation. The mean body height of our subjects also increased 0.87 cm during the study. We also had no complaints of low appetite from our subjects. Soon after the medication was discontinued, we observed that body weight increased significantly.

We assume that toleration of methylphenidate limited its effects on body growth during the study period, causing only temporary growth suppression. Several studies have documented inconsistencies in acute tolerance of methylphenidate and also long-term tolerance of its efficacy and side effects over time. They suggested that the tolerance effect of methylphenidate was a complex phenomenon requiring further study.

Our findings suggest that there were no significant side effects of methylphenidate administered for twelve weeks to children with ADHD. However, cardiovascular risks still need to be observed, especially during long-term use, as mentioned on the drug monograph. As a quasi-experimental study, we had no control subjects, which may limit the data interpretation. Future study with a larger sample size and longer observation would help us to better answer the clinical question. Overall, these study findings increased our understanding of psychopharmacology of stimulants on cardiovascular symptoms in children with ADHD, and of the adverse effects of this medication.

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