Long-Term Effects of Short-Acting Methylphenidate on Growth Rates of Children with Attention Deficit Hyperactivity Disorder at Queen Sirikit National Institute of Child Health

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Background: *Methylphenidate (MPH) is generally considered to be first-line treatment for the core symptoms of Attention Deficit Hyperactivity Disorder (ADHD). Long-term administration of MPH in childhood may have adverse effects on growth.*
Objective: *To determine the effect of long-term, short-acting MPH medication on growth.*
Material and Method: *A retrospective descriptive study was employed by gathering the data of patients who were diagnosed as ADHD by child psychiatrists at the child and adolescent clinic, Queen Sirikit National Institute of Child Health. Subjects were patients received the first dose of short-acting methylphenidate from January 1st, 2000 to December 31st, 2007 and continued medication for at least 1 year. Data about height and weight were reviewed at the beginning of short-acting MPH medication, 6 months (mo), 1 yr, 2 yr, 3 yr, 4 yr, 5 yr, 6 yr and 7 yr interval. Collecting data was interpreted with INMU-Nutri Stat software program. Paired t-test was used to compare Z score of height and weight at different time points.*
Results: *There were 96 cases in the present study; the ratio of male to female was 3.6: 1. The first dose of short-acting methylphenidate was started at an average age of 8.62 $\pm$ 1.70 years. Average drug dose ranged from 0.41-0.49 mg/kg/day. The data evaluated at 6 mo, 1 year, 2 years, 3 years, 4 years and 5 years after drug use found that weight was not affected. Height decreased at 6 mo. after drug use ($p < 0.05$) but long-term treatment was not statistically significant.*
Conclusion: *Prolonged medication with short-acting MPH has shown to have minimal impact on height only at the first 6 months; however, catch up growth was detected during adolescent period.*

Keywords: *Methylphenidate, Attention deficit hyperactivity disorder, Growth, Height, Weight*

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Attention Deficit Hyperactivity Disorder (ADHD) is the most common behavioral and neuropsychiatric disorder in school-age children. The core symptoms of ADHD consist of inattention, hyperactivity and impulsivity. Symptoms may persist into adulthood for up to half of children diagnosed with ADHD. Medical management combined with behavioral treatment is the most effective ADHD management strategy[1]. Psychostimulant medication is the medical treatment of choice in ADHD[2]. It has been shown in many studies to reduce the overall core symptoms of ADHD[3-6]. Methylphenidate (MPH) is the US Food and Drug Administration (USFDA) approved psychostimulant most widely prescribed to treat ADHD since 1960's[7]. It is also most widely used to treat ADHD children in Thailand as well. One of the adverse effects of MPH is appetite loss[8]. This adverse effect triggers parental concerns about the negative effects on growth. Researchers have also looked into the role of methylphenidate in affecting growth. Some studies found a slight decrease in height and weight acceleration[9-18]. Other studies have not indicated any significant effect on height and weight[19-22]. There are limited studies in the effect of growth suppression in Thai ADHD children who have taken long-term MPH

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medication[23,24].

In the present study, the authors aimed to analyze growth data including height and weight in Thai ADHD children who received long-term, short-acting MPH medication in order to see whether it caused growth suppression or not.

Material and Method

Study population

The present study was approved by the Ethics Committee of the Queen Sirikit National Institute of Child Health. It was a retrospective descriptive study. The authors included all patients who attended the Child and Adolescent Psychiatric clinic, Department of Child and Adolescent Psychiatry, Queen Sirikit National Institute of Child Health. The diagnoses were based on DSM-IV criteria of ADHD and each case was examined by child and adolescent psychiatrists. The inclusion criteria were: age 6 years and above, start short-acting MPH medication at any time between Jan 1st, 2000 to Dec 31st, 2007 and continuously taking the medicine at least 1 year. The exclusion criteria were: ADHD children who received other medications continuing more than 3 months and who had concomitant genetic or neurologic disorders. Height and weight data were collected at the beginning of short-acting MPH medication as a baseline data, 6 mo, 1 yr, 2 yr, 3 yr, 4 yr, 5 yr, 6 yr, 7 yr interval. The authors used INMU-Nutri Stat software program for interpreting nutritional status of 0 to 19 years old based on the Thai growth standard, Ministry of Public Health 1997 adjusted age for height and weight data. The results of three main nutritional indicators: weight for age (WA), height for age (HA) and weight for height (WH) of each individual child is presented in z-score. The characteristics of the population such as age, sex, drug doses were reported as well. Sample size was calculated using formula $\{N = t^2_{\alpha/2} \times p(1-p)\} / \alpha^2$ (α = margin of error at 5% (standard value of 0.05), p = estimated prevalence of ADHD which was 3.5-5%, t = confidence level at 95% (standard value of 1.96). The final sample size (N) required in the present study was between 51-73 persons.

Statistical analysis

Descriptive analysis was used to evaluate the demographic characteristics of the example and reported as raw number and proportion for categorical variables, as mean and standard deviation for numerical variable. Paired t-test was used to compare Z score of height and weight at different time points. Statistically significant differences were assumed if the p-value was < 0.05. Data were processed with SPSS software version 12.0.

Results

There were 96 patients included in the present study. All of them were diagnosed with ADHD combined type. Seventy-five children were male, 21 children were female. Male to female ratio was 3.6: 1. Mean age of the starting point of medication was 8.62 $\pm$ 1.70 years (Table 1). A drop out rate of more than 50% was observed from the 3rd year after the beginning of medication, and was obviously increasing every year. Unfortunately, it was not possible to collect intended data up through 5 years duration due to the unexpected high rate of drop out (Table 2). The mean weight-adjusted dose of short-acting MPH at 6 mo, 1 yr, 2 yr, 3 yr, 4 yr, 5 yr were 0.44, 0.48, 0.48, 0.49, 0.41, 0.42 mg/kg/day respectively. Average drug dose range was from 0.41-0.49 mg/kg/day.

The majority of the children in the present study had normal WA, HA and WH at the beginning of the study. Percentages of baseline WA, HA and WH of study population fell below average range were 9.4%, 6.3% and 10.4% respectively. Almost 10% of the population still continuously fell below average ranges in WA, HA and WH until the 3rd year after medication and all the children in this group caught up to average WA, HA and WH growth ranges at the 4th and 5th year after medication, except for HA that was still in slightly stunted range about 6.7% of population at the 4th year, however it returned within normal range around the 5th year (Table 2-4).

The difference in height and weight between each time period and the baseline in 3 domains were calculated into weight Z score (WA), height Z score

Table 1. Distribution of age that start short-acting MPH

Age	6-9 yr	9-12 yr	12-15 yr	Total
Number %	63 (65.6%)	28 (29.2%)	5 (5.2%)	96 (100%)
Mean $\pm$ SD	7.62 $\pm$ 0.83	10.14 $\pm$ 0.72	12.82 $\pm$ 0.54	8.62 $\pm$ 1.70

Table 2. Weight for age at different interval

	Weight for age					
	Under weight	slightly under weight	normal	Slightly over weight	Over weight	Total number
Baseline	3 (3.1%)	6 (6.3%)	71 (73.9%)	6 (6.3%)	10 (10.4%)	96
6 mo.	1 (1.4%)	5 (7.4%)	52 (76.5%)	4 (5.9%)	6 (8.8%)	68
1 yr	3 (3.6%)	5 (6.0%)	63 (76%)	5 (6%)	7 (8.4%)	83
2 yr	1 (1.8%)	4 (7.1%)	41 (73.3%)	4 (7.1%)	6 (10.7%)	56
3 yr	1 (3.6%)	2 (7.1%)	19 (67.9%)	2 (7.1%)	4 (14.3%)	28
4 yr	0	0	11 (73.4%)	2 (13.3%)	2 (13.3%)	15
5 yr	0	0	4 (66.6%)	1 (16.7%)	1 (16.7%)	6

Table 3. Height for age at different interval

	Height for age					
	stunt	slightly stunt	normal	above average	tall	Total number
Baseline	2 (2.1%)	4 (4.2%)	79 (82.3%)	5 (5.2%)	6 (6.2%)	96
6 mo.	1 (1.5%)	2 (2.9%)	58 (85.3%)	4 (5.9%)	3 (4.4%)	68
1 yr	2 (2.4%)	4 (4.8%)	68 (82%)	5 (6.0%)	4 (4.8%)	83
2 yr	1 (1.8%)	3 (5.4%)	47 (83.9%)	2 (3.6%)	3 (5.3%)	56
3 yr	1 (3.6%)	2 (7.1%)	23 (82.1%)	1 (3.6%)	1 (3.6%)	28
4 yr	0	1 (6.7%)	13 (86.6%)	1 (6.7%)	0	15
5 yr	0	0	5 (83.3%)	0	1 (16.7%)	6

Table 4. Weight for height at different interval

	Weight for height						
	wasting	slightly wasting	normal	Over weight	slightly obesity	obesity	Total number
Baseline	1 (1.0%)	9 (9.4%)	74 (77.1%)	3 (3.1%)	6 (6.3%)	3 (3.1%)	96
6 mo.	0	7 (10.3%)	54 (79.4%)	2 (2.9%)	3 (4.4%)	2 (2.9%)	68
1 yr	1 (1.2%)	8 (9.7%)	64 (77.1%)	3 (3.6%)	5 (6.0%)	2 (2.4%)	83
2 yr	0	6 (10.7%)	42 (75%)	2 (3.6%)	4 (7.1%)	2 (3.6%)	56
3 yr	1 (3.6%)	1 (3.6%)	20 (71.4%)	1 (3.6%)	3 (10.7%)	2 (7.1%)	28
4 yr	0	0	12 (80%)	1 (6.7%)	1 (6.7%)	1 (6.6%)	15
5 yr	0	0	5 (83.3%)	1 (16.7%)	0	0	6

(HA), and weight Z score (WH). The authors found that weight Z score (WA) , and (WH) slightly increased, after 6 mo, whereas from 1 yr, 2 yr, 3 yr, 4 yr, 5 yr of therapy, Z score decreased from baseline. However, an analysis at all interval did not show any statistical significant effects. Height Z score (HA) were less than baseline at 6 mo, 1 yr, and 3 yr interval, whereas during 2 yr, 4 yr, and 5 yr of therapy, Z score increased from baseline. An analysis of the change in height Z score (HA) show statistical significant effects only at 6 mo

Table 5. Change on height, weight Z score at different interval

	Mean Z score		Mean Paired Differences	p- value
	Baseline	medication		
Weight Z score (W/A)				
6 mo. (n = 68)	0.0244	0.0253	0.0009	0.985
1 yr (n = 83)	0.0101	-0.0600	-0.0701	0.195
2 yr (n = 56)	0.1996	0.0904	-0.1093	0.225
3 yr (n = 28)	0.2879	0.2118	-0.0761	0.524
4 yr (n = 15)	0.5753	0.3967	-0.1787	0.362
5 yr (n = 6)	0.6233	0.5183	-0.1050	0.517
Height Z score (H/A)				
6 mo. (n = 68)	0.0926	-0.0060	-0.0987	0.018*
1 yr (n = 83)	0.0847	0.0477	-0.0370	0.451
2 yr (n = 56)	0.0546	0.0605	0.0059	0.940
3 yr (n = 28)	-0.0539	-0.0850	-0.0311	0.784
4 yr (n = 15)	-0.0740	0.0187	0.0927	0.605
5 yr (n = 6)	0.0483	0.0717	0.0233	0.921
Weight Z score (W/H)				
6 mo. (n = 68)	-0.0568	0.0444	0.1012	0.191
1 yr (n = 83)	-0.0812	-0.1405	-0.0593	0.454
2 yr (n = 56)	0.2255	0.0507	-0.1748	0.162
3 yr (n = 28)	0.4779	0.3896	-0.0882	0.548
4 yr (n = 15)	0.9060	0.4547	-0.4513	0.091
5 yr (n = 6)	1.0933	0.6517	-0.4417	0.207

interval (Table 5).

Discussion

The ratio of male to female ADHD children in the present study was not different from worldwide distribution[25-27]. The medication was started around the 2nd-3rd grades because ADHD symptoms appear to cause negative effects to children's learning at those grade levels[28]. There were some children that had growth retardation (both in weight and height) prior to medication; this may be caused by either internal factors or other external factors, which were not measured in the present study. Growth retardation was observed throughout the 3rd year follow-up period and it was resolved afterwards. The loss of expected growth assessed in Z score showed that the effects of short acting MPH were limited only to height at the first 6 mo after initiating therapy, without any effects on weight. This data can be summarized as follows: prolonged medication with short-acting MPH had shown minimal impact on height only at the first 6 mo; however, it could catch up during the adolescent period while subjects are still continuously taking the medicine.

A number of limitations in the present study should be considered. First, the control group receiving no treatment was not included. Second, interpretation of the data could have been more carefully evaluated. Due to the high drop out rate after 3 years follow-up, the sample size at the end of the study was much less than the calculated sample size, so the data may not be adequately applicable to all ADHD children. Third, data regarding drug adherence and accumulative dose analysis could not be collected in the present study due to the nature of retrospective data collecting. Finally, other factors that can affect growth, such as diet and anemia, were not evaluated.

Conclusion

Prolonged medication with short-acting MPH showed minimal impact on growth only at the first 6 mo; however, growth could catch up in the adolescent period.

Potential conflicts of interest

None.

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ผลระยะยาวของการใช้ยา methylphenidate ชนิดออกฤทธิ์สั้นต่อการเจริญเติบโตของผู้ป่วยโรคสมาธิสั้นในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

ปราณี เมืองน้อย, ปริญญาพร ไหมแพง

***ภูมิหลัง**: Methylphenidate เป็นยาอันดับแรกที่ใช้ในการรักษาอาการของโรคสมาธิสั้นแต่การรักษาผู้ป่วยด้วยยา methylphenidate เป็นระยะเวลานานอาจมีผลลบต่อการเจริญเติบโตของเด็ก*

***วัตถุประสงค์**: เพื่อศึกษาผลระยะยาวของยา methylphenidate ชนิดออกฤทธิ์สั้นต่อการเจริญเติบโตของเด็กสมาธิสั้น*

***วัสดุและวิธีการ**: เป็นการศึกษาแบบ retrospective descriptive study ในผู้ป่วยเด็กที่ได้รับการวินิจฉัยโรคสมาธิสั้นที่เข้ารับการตรวจรักษาที่คลินิกจิตเวชเด็กและวัยรุ่นสถาบันสุขภาพเด็กแห่งชาติมหาราชินี และได้รับการรักษาด้วยยา methylphenidate ชนิดออกฤทธิ์สั้นอย่างน้อย 1 ปี โดยครั้งแรกที่เริ่มรับยาอยู่ระหว่างวันที่ 1 มกราคม พ.ศ. 2543 ถึง 31 ธันวาคม พ.ศ. 2550 นำข้อมูลความสูงและน้ำหนักที่ระยะเวลาหลังการเริ่มใช้ยา 6 เดือน 1 ปี 2 ปี 3 ปี 4 ปี และ 5 ปี มาแปลผลเป็น Z score เปรียบเทียบตามเกณฑ์อายุ ด้วยโปรแกรม INMU-Nutri stat ทำการวิเคราะห์ผลโดยใช้ paired t-test*

***ผลการศึกษา**: มีผู้ป่วยที่เข้าเกณฑ์การศึกษาทั้งหมด 96 คน อัตราส่วนเพศชายต่อเพศหญิงเท่ากับ 3.6: 1 อายุเฉลี่ยที่เริ่มรับยาเท่ากับ 8.62 $\pm$ 1.70 ปี ขนาดยาเฉลี่ยที่ใช้มีค่าระหว่าง 0.41-0.49 มก./กก./วัน ส่วนสูงของเด็กลดลงอย่างมีนัยสำคัญทางสถิติ เฉพาะที่ระยะเวลาหลังใช้ยา 6 เดือนเท่านั้น หลังจากนั้นไม่มีการเปลี่ยนแปลงของส่วนสูงอย่างมีนัยสำคัญทางสถิติ สำหรับน้ำหนักไม่พบการเปลี่ยนแปลงที่มีนัยสำคัญทางสถิติทุกช่วงเวลา*

***สรุป**: การใช้ยา methylphenidate ชนิดออกฤทธิ์สั้นเป็นระยะเวลานาน มีผลลบต่อความสูงเพียงช่วงสั้นๆ 6 เดือนหลังใช้ยาเท่านั้น ไม่มีผลระยะยาวต่อการเจริญเติบโตของเด็กสมาธิสั้นทั้งในด้านความสูงและน้ำหนัก*