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Effect of Methylphenidate on Sleep Parameters in Children with ADHD

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Objective The primary aim of this study was to investigate the acute impact of methylphenidate (MPH) on sleep parameters in attention-deficit/hyperactivity disorder (ADHD) children. The second aim was to investigate the different effects of intermediate- and long-acting MPH on sleep parameters. The third aim was to test the different effects of dose and age on sleep parameters.

Methods Ninety-three ADHD children were enrolled and randomized to two different MPH preparations. Baseline and daily sleep diaries were evaluated for four weeks after taking medication. Weekday and weekend bedtimes, wake-up times, sleep latencies and total sleep times were compared by weeks.

Results After taking MPH, there was a significant delay in bedtimes and a significant reduction of total sleep time (TST) both on weekdays and at weekends. There was also a significant delay in wake-up time on weekdays. However, the difference was applied to younger age group children only. There was no difference in changes of TST between metadate-CD and OROS-MPH. There also was no difference in changes of TST with different doses of MPH.

Conclusion MPH had negative impacts on sleep among young ADHD children, but different preparations and doses did not affect the result.
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Key Words ADHD, Children, Methylphenidate, OROS-MPH, Metadate-CD.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood central nervous system (CNS) disorders and is estimated to occur in 3-7% of school aged children.[1] In treating ADHD, methylphenidate (MPH) is the most frequently prescribed medication, and nearly 70-80% of children with ADHD are treated with stimulants alone or in combination with other treatment modalities.[2] MPH mainly blocks the reuptake of dopamine and, to a lesser extent, norepinephrine, from presynaptic vesicles in the central nervous system.[3] It has been approved by the U.S. Food and Drug Administration as a first-line treatment for children, adolescents, and adults with ADHD.[4]

Although MPH is known to be relatively well-tolerated, adverse effects such as appetite reduction, nervousness, headache, irritability, anxiety, and nail biting are prevalent. MPH also has a negative effect on sleep, due to either a direct or a secondary "rebound" effect.[5-8] In one study, nearly a third of ADHD children who were treated with stimulant increased sleep latency or insomnia every night.[9] Two night of polysomnographic study with 27 ADHD children reported that MPH prolonged sleep latency by 29 minutes and shrotened sleep duration by 1.2 hours.[10] However, there are studies that report MPH does not affect negatively on sleep. In an open-label, randomized study of 26 ADHD children, MPH did not affect sleep latency and total sleep time.[11] Kim et al.[12] also reported that MPH reduced nighttime awakening and parasomnic events.

Children's sleep is important because children with sleep difficulties are likely to become easily frustrated and experience emotional difficulties such as restlessness and irritability, and sleep restriction has been shown to impair executive (e.g., plan-

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ning, organization, and problem solving), cognitive (e.g. attention and inhibition) and behavioral (e.g., irritability, low frustration tolerance) functioning.[13-15] The sequelae of sleep disturbances are similar to the symptom of ADHD, and can exacerbate the existing symptoms of ADHD.[16] There is growing research focusing on the sleep of children with ADHD because qualities and quantities of ADHD children's sleep affect their quality of life.

The primary aim of this study is to investigate changes in four sleep parameters associated with the two MPH preparations. The secondary goal is to check whether there are differences in sleep parameters between intermediate- and long-acting MPHs. The last aim was to evaluate the different effects of dose and age on sleep parameters.

METHODS

Subjects

The subjects for this study were 6-12 year old elementary school children with a diagnosis of ADHD, who were recruited and enrolled in three university hospitals in Korea during the period 1 September 2009 to 31 August 2010.

Fourth edition, text revision of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) was used in evaluation of psychiatric disorders. And modified version of Tucson Children's Assessment of Sleep Apnea Questionnaire (M-TuCASA) was used in evaluation of sleep problems of the subjects.

Children, whose ADHD accompanied by anxiety disorder, oppositional defiant disorder, or conduct disorder were included in the study, but patients with tic disorder, Tourette syndrome, schizophrenia, bipolar disorder, major depressive disorder, obsessive-compulsive disorder or a pervasive development disorder were excluded. Also excluded from the study were those with an IQ below 70, epilepsy or other neurological problems, and those who had been taking stimulants, antidepressants, antipsychotics, atomoxetine, clonidine, and antihistamine within four weeks of baseline evaluation because these medications can affect sleep.

Finally, subjects were excluded if they were confirmed to have sleep problems such as heavy snoring, sleep apnea, sleep bruxism, narcolepsy, restless legs syndrome, and periodic limb movement disorder. Subjects were dropped from the study if they violated the study protocol by failing to take the prescribed medicine more than twice a week, or if they presented with serious adverse effects such as seizures or hallucinations.

Written informed consent was provided by one or both of the parents/guardians, and also by all the subjects. The study protocols were reviewed and approved by each site's Institutional Review Board.

Study design and procedures

This was a 4-week, randomized, phase IV, parallel-group study. Screening involved the diagnosis of psychiatric disorders other than ADHD and the administration of the Korean Wechsler Intelligence Scale for Children-III (K-WISC-III), the Korean version of the Swanson, Nolan and Pelham version IV (SNAP-IV), the Clinical Global Impression-Severity (CGI-S), and sleep problem questionnaires, in addition to the collection of demographic data and the evaluation of medical and psychiatric histories. The diagnosis of psychiatric disorders of the subjects was based on DSM-IV-TR and the Korean version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL).[17,18] M-TuCASA was used in evaluation of sleep problems.[19] M-TuCASA was translated into Korean and it was validated in the previous study.[20] M-TuCASA was composed of 21 questions and it was for evaluating snoring, sleep apnea, sleep bruxism, enuresis, daytime fatigue, nightmares and sleep terrors. A baseline assessment using weekday and weekend sleep diaries was implemented 7 days before administration of MPH. The sleep diary was based on the one used in the previous field study.[20]

Using a randomization code, the subjects were randomly assigned to take either OROS-Methylphenidate(MPH) or Metadate-CD. The recommended initial doses were 18 mg for OROS-MPH and 10mg Metadate-CD and all were instructed to take their medication at around 8 a.m. Dosage was then adjusted using a flexible dosing strategy according to the patient's clinical improvement and tolerability. The goal dose range and the maximum dose were 0.4-1.8 mg/kg and 72 mg for OROS-MPH and 0.6-1.5 mg/kg and 60 mg for Metadate-CD. The subjects and their parents/guardians visited weekly for a review of whether the medication was being taken as prescribed, to adjust dosages, and for assessments on the Clinical Global Impression of Severity (CGI-S) and the Clinical Global Impression-Improvement scale (CGI-I).

The parents/guardians were asked to complete the sleep diary daily for 7 days before medication and for the four weeks after taking MPH. In the sleep diary, a detailed record was kept of medicine administration regularity, bedtime, sleep latency, wake-up time, daytime naps and their durations were documented daily. Also recorded were children's day and night activities such as schedule of going to school and coming back from school, a list of extracurricular activities and their schedule, homecoming time, hours of watching TV and using a computer, and the hours spent studying.

Adverse events (AEs) chart was used to assess the side effects of two different medications. It was completed by the basis of direct questions, clinical observations and physical examinations of child psychiatrists at the weekly session. AEs were for

checking depression, anxiety, headaches, sedation, palpitations, chest discomfort, appetite loss, dyspepsia, nausea, dry mouth, irritability, aggressiveness, nail biting, tics, and delusions or hallucinations of subjects. And any relationship of these to the medications was also checked in AEs. If patients chose to withdraw from the study, the reason for this was sought and documented.

Statistical analyses

Student's t-tests were performed to compare differences between the two groups on the demographic variables. Repeated measures ANOVAs and Fisher's least significant difference (LSD) tests were used to compare bedtime, wake-up time, total sleep time, and sleep latency measures at baseline and at each of the following weeks'. Student's t-test was also performed to determine any difference in total sleep time between two different stimulants. The last observation carried forward (LOCF) was used to replace missing data, and statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS version 17.0 for Windows.

RESULTS

Demographic data

A total of 63 (67.7%) of 93 subjects completed all processes: 31 (67.4%) of 46 subjects completed in the OROS-MPH group, and 32 (68.1%) of 47 completed in Metadate-CD group. There was no difference in drop-out rates between the two groups.

Thirty subjects dropped out for the following reasons: lost to follow-up (14 subjects, 47%), protocol violation (9 subjects, 30%), identification of concomitant Tourette's syndrome after baseline evaluation (5 subjects, 17%), parental withdrawal of participation (1 subject), and withdrawal due to side-effect of medication (1 subject).

Most of the children (n=56, 88.9%) were male. The mean age of all subjects was 8.58±1.61 years, and the mean IQ was 96.39±17.01. The combined type of ADHD (53 subjects, 84.1%) was the most common. The mean score on the SNAP-IV was 25.44±9.89 at baseline, and this decreased to 15.03±8.66 after using MPH for four weeks. The mean total sleep time for all subjects at baseline was 8 hours 49 minutes on weekdays and 9 hours 14 minutes at weekends.

The mean BMI of the OROS-MPH group (18.62±3.56) was significantly higher than for the Metadate-CD group (17.07±2.46) ($p<0.05$), and there was also a significant difference ($p<0.001$) in the initial doses of MPH (although not at the endpoint). There were no differences between the two groups in the demographic variables of age, gender ratio, or intelligence (Table 1).

Comparison of sleep parameters

We compared the overall changes in the four sleep param-

Table 1. Demographic data of the participants (N=63)

	Total	OROS-MPH Mean (SD)	Metadate-CD Mean (SD)	t	Sig.
Age (years)	8.58 (1.61)	8.81 (1.42)	8.37 (1.74)	1.06	0.292
Gender*					
Boys	56	27	29	0.19	0.708
Girls	7	4	3		
IQ	96.39 (17.01)	94.07 (16.07)	98.56 (17.81)	-1.04	0.302
BMI	17.83 (3.12)	18.62 (3.56)	17.07 (2.46)	2.01	0.049
SNAP-IV					
Baseline	25.44 (9.89)	26.06 (9.75)	24.84 (10.13)	0.49	0.628
Endpoint	15.03 (8.66)	15.29 (9.56)	14.78 (7.84)	0.23	0.818
Total sleep time (baseline)					
Weekdays (h:m)	8:49 (0:51)	8:44 (0:53)	8:53 (0:48)	-0.65	0.514
Weekends (h:m)	9:14 (1:02)	9:12 (1:02)	9:17 (1:02)	-0.29	0.775
Dose					
Initial (mg)	14.50 (5.09)	19.16 (3.07)	10.00 (0.00)	16.90	0.000
(mg/kg)	0.47 (0.21)	0.62 (0.22)	0.34 (0.07)	6.76	0.000
Endpoint (mg)	31.09 (8.58)	32.23 (11.23)	30.00 (5.08)	1.03	0.307
(mg/kg)	0.99 (0.25)	0.97 (0.28)	1.02 (0.21)	-0.88	0.380

*chi-square test. h:m: hours:minutes, IQ: intelligence quotient, BMI: body mass index, SNAP-IV: Swanson, Nolan and Pelham Questionnarie, OROS-MPH: Osmotic release oral system-methylphenidate

eters on weekdays and at weekends before and after using MPH. On weekdays, the mean bedtime was 10:06 pm before taking MPH and 10:23 pm in the first week with MPH [p< 0.001, effect size (ES): 0.11]. This change and the changes of each week were statistically significant (p<0.001). The mean wake-up time was 7:13 am before medication and 7:18 am in first week with MPH. This difference was not significant. However, wake-up times were significantly later compared with baseline from the second to fourth week (p<0.001, ES: 0.09). The mean total sleep time was 8 hours 49 minutes before using MPH and significantly decreased to 8 hours 31 minutes in first week with medication(p<0.001, ES: 0.08). The TST difference between baseline and each week were significant (p<0.001). Sleep latencies showed no significant changes over the study period.

At weekends, the changes in bedtimes and total sleep times were similar to those on weekdays. The mean bedtimes for each week after MPH were significantly later than the mean bedtime at baseline (p<0.001, ES: 0.08). The mean total sleep times showed a similar trend and were significantly lower than at baseline for each week after MPH (p<0.01, ES: 0.12). Compared with baseline, there were no significant changes in either wake-up times or sleep latencies at weekends. Where a significant change arose in the mean value of a sleep parameter before and after MPH, there were no significance differences between the mean values over subsequent weeks. (Table 2, Figure 1).

Changes in total sleep time according to types of MPH, age and dose per kilogram of MPH

The baseline TST was 8 hours 44 minutes for the OROS-MPH group and 8 hours 53 minutes for the Metadate-CD group; this difference was not significant. There were also no significant differences in TST between two medications at each week following baseline. In the OROS-MPH group, the mean TST was significantly less than baseline at each week (p<0.05, ES: 0.09) except the second week, and it was 18 minutes less than baseline at the fourth week. For the Metadate-CD group there were significant decreases in the mean TST compared with baseline at only the first and third week (p< 0.05, ES: 0.08), and while there was 17 minute decrease in the fourth week compared with baseline, this change was not significant (Table 3).

The average dose per kilogram of medications administered to the subjects was 1.00±0.25 mg/kg, and this was used as the basis for dividing the subjects into lower and higher dose groups. After baseline, there was an 11-21 minute decrease in TST for the lower dose group and a 16-25 minute decrease in TST for the higher dose group(p<0.05, ES: 0.10). There were no significant differences in TST changes between the lower and higher dose groups (Table 4).

The participants were divided into three groups by age: younger (6-8 years), middle (9-10 years), and older (11-12 years) age groups. The younger age group showed significant changes in mean TST from the first week after baseline (p<0.001, ES: 0.22) and there was a decrease of about 30 minutes in the fourth week compared with baseline. However, the middle and older age groups showed no significant changes in TST. When dose per kilogram was used as a covariate, a significant difference in TST changes remained with the younger age group showing a greater decrease in TST than the middle age group [$F_{(2, 60)}$=4.31, p<0.05] (Table 5).

DISCUSSION

The aim of this study was to evaluate the effect of MPH, which is one of the most commonly used ADHD medications, on sleep using a sleep diary. Most previous studies compared sleep

Table 2. Sleep parameters for the baseline and each four weeks of methylphenidate trial (N=63)

	Baseline Mean (SD)	1st week Mean (SD)	2nd week Mean (SD)	3rd week Mean (SD)	4th week Mean (SD)	F-value	Sig.	ES
Weekdays								
Bedtime	22:06 (0:53)	22:23 (1:02)*	22:28 (0:38)*	22:26 (0:58)*	22:40 (1:01)*	7.83	0.000	0.11
Wake-up time	7:13 (0:33)	7:18 (0:32)	7:22 (0:25)*	7:21 (0:25)*	7:25 (0:25)*	5.85	0.001	0.09
Total sleep time (h:m)	8:49 (0:50)	8:31 (0:44)*	8:33 (0:38)*	8:26 (0:49)*	8:31 (0:53)*	5.57	0.001	0.08
Sleep latency (h:m)	0:19 (0:16)	0:23 (0:24)	0:21 (0:15)	0:22 (0:19)	0:20 (0:16)	1.32	0.270	0.022
Weekends								
Bedtime	21:20 (1:01)	22:38 (0:54)*	22:48 (0:51)*	22:39 (0:57)*	22:40 (0:48)*	5.02	0.002	0.08
Wake-up time	7:55 (1:02)	7:44 (0:41)	7:43 (0:41)	7:53 (1:11)	7:51 (0:45)	0.77	0.507	0.02
Total sleep time (h:m)	9:14 (1:02)	8:43 (0:56)*	8:35 (0:54)*	8:48 (0:58)*	8:43 (1:05)*	7.00	0.000	0.12
Sleep latency (h:m)	0:18 (0:16)	0:20 (0.16)	0:18 (0:11)	0:19 (0:17)	0:20 (0:17)	0.57	0.683	0.01

*p<0.05 comparisons with baseline. n: number, h:m: hours:minutes, ES: effect size

variables with baseline and at a certain time after using MPH, but this study compared quantitative changes in sleep variables after using MPH with daily sleep diary records. We expect that the results of this study will be useful in clinical situations.

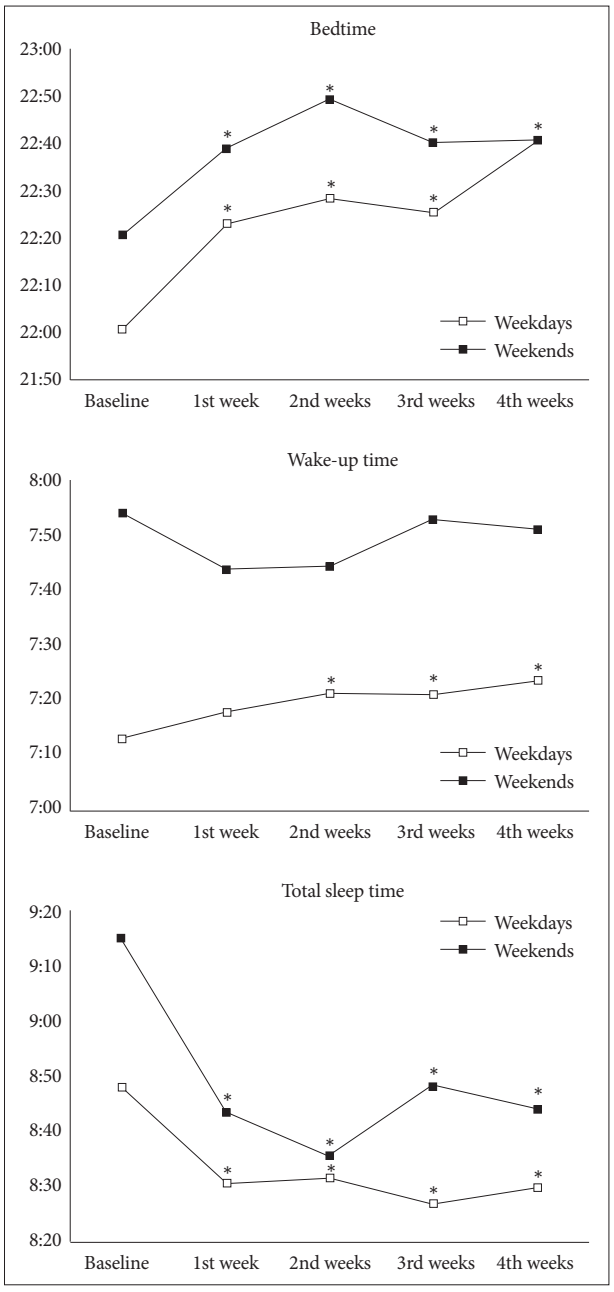

Figure 1. Changing patterns of sleep parameters for four weekdays and weekends. *p<0.05 comparisons with baseline.

The major finding of this study was that MPH had a negative effect on bedtimes, wake-up times and total sleep times. Previous studies have reported similar findings. In an actigraphic study of 21 ADHD children over a three week period, MPH decreased TST by about 60 minutes and caused significant changes in light-out time and sleep onset time.[21] In a double-blind, placebo-controlled, crossover study with 44 ADHD children, MPH also caused an increase in sleep onset latency and a decrease in total sleep time and sleep efficiency.[22] Although the present study showed that MPH had negative effects on sleep, which were similar to those, found in previous studies, some results were different. TST was reduced by about 17 minutes on weekdays and 29 minutes at weekends. These reductions in TST were less than those in other studies.[21,23] We presumed that when we measured TST every day the quantitative changes of TST was not actually big even those changes were statistically significant. Furthermore, unlike the findings of the other studies, sleep latency did not change. We suggest the reason was that bedtime was not fixed as the usual time for being put to bed. Also, it is possible that sleep diary itself is not to be sensitive to small change such as sleep latency.

In considering decrease of TST, it was only applied to younger age group. Although TST of older age group was decreased about 30 minutes, it was not significant. The result was same when the dose per kilogram was used as a covariate. Previous studies have reported mixed results. Sangal et al.[8] found that a younger age group of children showed more delay in sleep onset latency. In the polysomnographic study with 24 ADHD children, Kim et al.[12] reported that younger children had more sleep complaints, and age was a factor related to sleep onset delay and sleep onset latency. However, Faraone et al.[23] in their double-blind, multicenter, parallel-group study of 6-12 year old ADHD children reported that children's age did not influence the severity of sleep problems and that it was not an important factor in causing sleep problems. The results of this study indicate that younger ADHD children are vulnerable to the sleep-related side effects of MPH. In clinical setting, we should be more careful with prescription MPH to young ADHD children.

The second finding of this study was that, although there were significant differences in the sleep parameters before and after the baseline week, there were no significant changes over

Table 3. Comparison of changes in total sleep time between OROS-MPH and metadate-CD for four weekdays

	Baseline Mean(SD)	1st week Mean(SD)	2nd week Mean(SD)	3rd week Mean(SD)	4th week Mean(SD)	F-value	Sig.	ES
OROS-MPH (h:m) (N=31)	8:44 (0:53)	8:28 (0:47)*	8:31 (0:35)	8:25 (0:52)*	8.26 (0:47)*	2.83	0.028	0.09
Metadate-CD (h:m) (N=32)	8:53 (0:48)	8:34 (0:40)*	8.36 (0:40)	8:29 (0:47)*	8:36 (0:59)	2.75	0.045	0.08

*p<0.05 comparisons with baseline. n: number, h:m: hours:minutes, ES: effect size, OROS-MPH: Osmotic release oral system-methylphenidate

Table 4. Comparison of changes in total sleep time between low- and high-dose groups of methylphenidate for four weekdays

	Baseline Mean(SD)	1st week Mean(SD)	2nd week Mean(SD)	3rd week Mean(SD)	4th week Mean(SD)	F-value	Sig.	ES
Lower-dose (h:m) (N=27)	8:32 (0:50)	8:16 (0:46)	8:21 (0:41)	8:15 (0:54)	8:11 (0:50)	2.27	0.067	0.08
Higher-dose (h:m) (N=36)	9:01 (0:48)	8:43 (0:38)*	8:43 (0:32)*	8:36 (0:44)*	8:46 (0:53)	3.80	0.011	0.10

*p<0.05 comparisons with baseline. n: number, h:m: hours:minutes, ES: effect size

Table 5. Comparison of changes in total sleep time between age groups for four weekdays

	Baseline Mean (SD)	1st week Mean (SD)	2nd week Mean (SD)	3rd week Mean (SD)	4th week Mean (SD)	F-value	Sig.	ES
Younger age group (h:m) (N=31)	9:20 (0:40)	8:51 (0:36)*	8:47 (0:32)*	8:46 (0:47)*	8:50 (0:53)*	8.25	0.000	0.22
Middle age group (h:m) (N=24)	8:18 (0:44)	8:19 (0:42)	8:23 (0:41)	8:14 (0:41)	8:22 (0:47)	0.42	0.792	0.02
Older age group (h:m) (N=8)	8:19 (0:30)	7:53 (0:43)	8:12 (0:29)	7:54 (0:54)	7:45 (0:40)	1.94	0.132	0.22

Younger age group: 6, 7, 8 years, Middle age group: 9, 10 years, Older age group: 11, 12 years. *p<0.05 comparisons with baseline. n: number, h:m: hours:minutes, ES: effect size

the weeks of MPH after the baseline week. This was the case even though a flexible dosing strategy was adopted, dosages were titrated in each week, and the dose per kilogram increased. Furthermore, even when the participants were divided into lower and higher dose groups, there were no significant differences in TST changes between these two groups. Several studies of sleep parameters according to duration and dose of MPH have reported similar results. In a polysomnographic study of 24 ADHD children, those with and without sleep complaints did not differ in the mean doses of OROS-MPH.[12] In study of 21 children with ADHD using an immediate release (IR) MPH total sleep time did not differ according to the dose, although it was significantly decreased compared with placebo.[21] A placebo and IR-MPH study of 40 children with ADHD reported that, although the severity of insomnia differed between the placebo and IR-MPH groups, it was unrelated to dose of IR-MPH.[6] Another study suggested that, even though the use of MPH had negative effects on the sleep of ADHD children, variables such as duration and dose of MPH did not significantly affect the sleep parameters.[21] However, generalization of this finding should be careful because this study was conducted over only four weeks.

The third finding was that there was no difference in TST between an intermediate- and long-acting MPH. Metadate-CD and OROS-MPH were both taken once a day but each medication had characteristic pharmacokinetics. 30% was immediate-release (IR) MPH and 70% was extended-relaed (ER) MPH in Metadate CD. It took 1.5 hours and 4.5 hours to reach peak concentration and half-life was 6 hours.[24] OROS-MPH is a medication which delivers MPH using by osmotic pressure. One hour after taking, it reached initial maximum concentration and there was a gradual ascending concentration in 5-9 hours.[25]

Until now, there has been a lack of studies on the differential effect of the two MPH preparations. Pelham et al.[26] reported that there was no difference in sleep parameters between three times a day IR- MPH and once a day OROS-MPH in the study of 68 ADHD children. It can be assumed that there were factors, other than direct effect of MPH itself, which have effects on children's sleep. One example is rebound hyperactivity, which is related to a decrease in MPH concentration.[5,22] More researches of MPH preparations of action duration need to ensure whether the negative effect of MPH on sleep are caused by a direct effect or a rebound hyperactivity.

This study has some limitations. Firstly, we used a sleep diary rather than objective measures such as actigraphy or polysomnography. Data yielded by a sleep diary, which relies on the validity of parents' observations, may not be an accurate representation of reality. Secondly, this study used a flexible titration method and did not divide the subjects into parallel-groups from the beginning in terms of, for example, dose of MPH and age. Third, lack of blinding is also a limitation of this study. Fourth, about more than 30% of the subjects did not complete this procedure and there was a possibility that this uncompleted procedure affected to the result.

Despite these limitations, this study confirms that MPH has negative impacts on sleep parameters in younger ADHD children, and that these negative effects are not related to type of MPH preparations or dosages within the therapeutic range. We expect future studies which are more structured and research longer term effect about sleep parameter depending on dose and preparations of MPH.

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