Switching from Methylphenidate-Immediate Release (MPH-IR) to Methylphenidate-OROS (OROS-MPH): A Multi-center, Open-label Study in Korea

Bung-Nyun Kim¹, Ye-Ni Kim², Un-Sun Cheong³, Jae-Won Kim¹, Jun-Won Hwang⁴, Min-Sup Shin¹, Soo-Churl Cho¹; Korean OROS-MPH Study Group

¹Division of Child & Adolescent Psychiatry, Department of Psychiatry, College of Medicine, Clinical Research Institute, Institute of Behavioral Medicine, Seoul National University, ²Department of Adolescent Psychiatry, National Center for Child and Adolescent Psychiatry, Seoul National Hospital, ³Department of Psychiatry, College of Medicine, Kyungpook National University, ⁴Department of Psychiatry, College of Medicine, Eulji University, Seoul, Korea

Objective: The objective of this study was to evaluate the efficacy and safety of methylphenidate HCL OROS extended-release (OROS-MPH) among children with attention deficit hyperactivity disorder (ADHD) who had been previously treated with methylphenidate HCL immediate-release (MPH-IR).

Methods: The sample included 102 children aged 6–12 (9.4 ± 2.6) years who had been diagnosed with ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM–IV; American Psychiatric Association, 1994) and who were attending seven centers in Korea. All participants had been medicated with a stable dose of MPH (10–60 mg/day) for at least 3 weeks before entry into the study. Doses of OROS-MPH were comparable to daily doses of MPH. Efficacy was assessed at baseline (day 0) and at day 28 with the Inattentive–Overactive with Aggression (IOWA) Conners Rating Scale, which was completed by parents/caregivers and teachers, the Peer Interaction Rating Items, which were completed by teachers, and the Clinical Global Impression (CGI) scale, which was completed by child psychiatrists. Paired t-tests were used, and P-values were set at the 0.05 level.

Results: Of the subjects, 92.2% were boys and 79.4% were students in the first to fourth grades of elementary school. 72% were diagnosed with the combined type of ADHD, 23% were diagnosed with the inattentive type, and 5% were diagnosed with the hyperactive–impulsive type. The results of the parents' responses to the Inattention/Hyperactivity (I/H) and Oppositional/Defiant (O/D) subscales of the IOWA Conners scale indicated statistically significant improvement in children's behavior after 4 weeks of treatment with OROS-MPH ($t=6.28$, $p<.001$, $t=4.12$, $p<.001$). However, the teachers' responses to the Conners I/H and O/D subscales indicated no significant improvement at 4 weeks. The teachers also reported no significant improvements under the OROS-MPH compared with the MPH-IR condition with respect to peer interactions. Scores on the CGI scale showed that 46.1% of children with ADHD were rated by psychiatrists as “minimally improved”, 27.5% as “much improved”, 1.0% as “very much improved”, 3.9% as “minimally worse”, and 16.7% as showing “no change”. Children exhibited significantly fewer tics with OROS-MPH treatment than with MPH-IR treatment (19.6% vs. 27.7%). We found no differences between in sleep and appetite problems according to medication.

Conclusion: The results of this study indicated that an MPH-IR regimen can be successfully changed to a once-daily OROS-MPH regimen without any serious adverse effects. The changes in parent/caregiver IOWA Conners ratings suggested that OROS-MPH improved the control of symptoms after school, a finding that is consistent with the 12-h duration of action of this medication. Because the therapeutic effect of OROS-MPH is sufficiently longer than that of a b.i.d. dose of MPH-IR, OROS-MPH had significant positive effects on oppositional/defiant behavior in addition to its effects on the core symptoms of ADHD.

KEY WORDS: Attention deficit hyperactive disorder; Methylphenidate IR; OROS-MPH, Switching.

INTRODUCTION

Received: June 23, 2010 / **Revised:** February 28, 2011

Accepted: March 11, 2011

Address for correspondence: Soo-Churl Cho, MD, PhD
Division of Child & Adolescent Psychiatry, Department of Psychiatry, Clinical Research Institute, Seoul National University Hospital, 101 Daehakro, Chongro-gu, Seoul 110-744, Korea
Tel: +82-2-2072-3648, Fax: +82-2-763-0253
E-mail: soochurl@snu.ac.kr

Attention deficit hyperactivity disorder (ADHD) constitutes one of the most common neurobehavioral disorders among children, affecting 3–5% of the school-age population.^{1–3)} In Korea, 7–10% of all students in elementary school have been diagnosed with ADHD.^{4,5)} This disorder is characterized by hyperactivity, impulsiveness,

and a developmentally inappropriate lack of attention. The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) requires that these symptoms appear before the age of 7, that they be present in two or more settings, and that they cause significant functional impairment.⁶⁾

Treatment typically requires a multimodal approach that includes psychosocial, behavioral, and medical interventions.⁷⁾ Studies of the multimodal treatment of ADHD (MTA) have shown that medication seemed to be an essential component of treatment, whereas the value of psychosocial interventions was questionable.⁸⁾ The Korean practice guidelines, however, emphasize the importance of a multimodal treatment approach to work with children with ADHD and their families.⁹⁾ The first line of pharmacotherapy for children with ADHD is stimulants such as methylphenidate (MPH) and dextroamphetamine.⁹⁾

The immediate-release forms of MPH (MPH-IR) have been widely used and have been found to be effective in about 75% of patients. However, the half-life of methylphenidate is very short, only 2-3 hours, and the pharmacodynamic half-life of the drug, as assessed by behavior ratings in school, is also very short.⁸⁾ Thus, children usually take morning and midday doses to cover school activities, and many children receive an after-school dose to cover the evening hours.

Another problem with the brevity of the effect of MPH-IR relates to patient compliance with midday and late-afternoon dosing. B.i.d. or t.i.d. regimens have led to poor adherence to treatment regimens. Studies of adherence to MPH-IR treatment regimens in Korean children with ADHD have shown that only 40% of patients took their midday or afternoon medication as prescribed.¹⁰⁾ Indeed, many children with ADHD want to avoid taking medication during school hours. Given the absence of nurses in many schools in Korea, children with ADHD must self-administer their medication, which renders compliance very unreliable.

Administration of a third daily dose of MPH-IR, typically after school, is made difficult by the possibility that children may be attending after-school child care or other extracurricular activities (e.g., academic activities) when the last dose should be administered. Professional consensus has identified problematic peer interactions as one of the major difficulties faced by children with ADHD. When this finding is coupled with data showing that stimulant medications have beneficial acute effects on peer interactions in recreational settings, the potential im-

portance of a later afternoon dose of medication for the treatment of impairments in peer settings is highlighted.¹¹⁾

Moreover, awareness that children with ADHD are impaired in their ability to perform homework tasks and that they engage in more conflict with parents has also been increasing.¹²⁾ The goal of ameliorating impaired at-home activities had led to a growing tendency in Korea to prescribe a third daily dose of MPH-IR in the late afternoon. Indeed, according to a previous study, 28% of children diagnosed with ADHD in Korea followed a t.i.d. dosing regimen.¹⁰⁾

OROS-MPH is a once-daily controlled-delivery methylphenidate product that is designed to deliver the drug at an increasing rate and to have a post-dosing effect of 12 hours.

Although several European researchers have conducted studies on the effects of switching from MPH-IR to OROS-MPH,^{13,14)} very few studies on this issue have been conducted in Asia thus far.

We conducted this study to investigate the efficacy and tolerability of OROS-MPH when children and adolescents treated for ADHD were switched from MPH-IR to the study medication. These children and adolescents were stable on their pre-study MPH-IR treatment regimen.

METHODS

Subjects

Participants were recruited using a number of methods, including advertisements and physician and parental referrals.

Diagnostic information was obtained during clinical interviews with the patients and their parents conducted by expert child psychiatrists. The diagnosis of ADHD was based on the DSM-IV criteria for this disorder. The symptoms of all participants were sufficiently severe to require medication with MPH upon entry into the study; all participants had been on a daily dose of MPH-IR for at least 4 weeks and had been receiving a stable dose for at least 3 weeks before beginning the study. Total daily doses ranged from 10 to 60 mg (mean dose: 25 mg; daily mean mg/kg dose: 0.75, SD: 0.34), with 64% of the sample population on a b.i.d. and 36% on a t.i.d. dosing schedule.

Exclusion criteria included the following: the presence of any medical condition that would contraindicate the use of stimulant medication; the presence of hypersensitivity to MPH; the presence of severe learning difficulties (e.g., IQ below 75 as determined by the Wechsler Intelligence

Scale for Children at screening); the use of any additional medication (other than MPH) for ADHD; the use of any medication having CNS effects (monoamine oxidase inhibitors, clonidine, tricyclic antidepressants, SSRIs, theophylline, coumarin or anticonvulsants, and antipsychotics) or any investigational medications; having reached menarche; having a high risk of being pregnant; and the presence of clinically significant gastrointestinal problems (e.g., small-bowel inflammatory disease), cystic fibrosis, glaucoma, seizure disorders, Tourette's syndrome, cardiovascular disease, hyperthyroidism, clinical depression, suicide risk, and substance abuse. Ultimately, a total of 102 patients from seven centers in Korea were enrolled in the study.

This study was approved by the Institutional Review Board for human subjects at Seoul National University Hospital in Korea. Parents of the participants gave their informed consent for their children's participation, and the children also assented to participation in the study procedures.

Dosing

Prior to entry into this clinical trial, all subjects had been on a daily MPH-IR dose (10-60 mg/day) for at least 4 weeks and had been stabilized on their current dose for at least 3 weeks, indicating that this dose had been effective for symptom control and had not been associated with unacceptable significant drug-related adverse events.

Subjects were assigned to one of three OROS-MPH doses [18, 36, or 54 mg once daily (od)] based on their pre-study dose of MPH-IR. Subjects receiving 5 mg of MPH-IR b.i.d. or t.i.d. were assigned to the OROS-MPH 18-mg od group; subjects receiving 10 mg of MPH-IR b.i.d. or t.i.d. were assigned to the OROS-MPH 36-mg od group; and subjects receiving 15 mg of MPH-IR b.i.d. or t.i.d. or a total daily dose of >45-60 mg were assigned to the OROS-MPH 54-mg od group. Clinical judgment was used to select the starting dose for subjects on other MPH regimens. Doses could be adjusted among these three levels at study visits on days 7 and 14 based on safety and efficacy observations made by the investigator.

Through this process, the total daily dose of MPH was increased in most patients. The dose of MPH before entering the study was 10-60 mg/day (mean 25.26 mg; SD 9.76), and 53.9% (55/102) of the final doses of OROS-MPH were 18 mg/day, 38.2% (39/102) were 36 mg/day, and 7.8% (8/102) were 54 mg/day.

Efficacy Measures

Primary efficacy measure

The Inattention/Overactivity (I/O) subscale of the IOWA Conners Rating Scale was completed by teachers and parents/caregivers at baseline (day 0) and day 28. Each item was rated on a 4-point scale from 0 (not at all) to 3 (very much). Scores for each subscale were summed separately (i.e., scores ranged from 0 to 15 on the I/O subscale), with lower scores indicating fewer ADHD symptoms.

Secondary efficacy measures

The Oppositional/Defiant (O/D) subscale of the IOWA Conners Rating Scale was completed by teachers and parents/caregivers, the Peer Interaction Rating Items were completed by teachers, and the Clinical Global Impression (CGI) Scale was completed by child psychiatrists. All assessments were completed at day 0 and day 28.

Safety Measures

All subjects received a screening physical examination at baseline and on day 28. The subjects' height and weight were also measured.

Adverse events were documented at each visit by recording spontaneous reports of adverse events and asking parents/caregivers about the quality of their child's sleep, their children's appetite during the past week, and whether their children had experienced tics during the past week. Investigators provided the parents with information and simple guideline for assessing the severity of tics.

Parents/caregivers rated sleep quality using a 4-point scale (poor, fair, good, excellent) and rated appetite using a 3-point scale (less than before-poor, same as before-fair, more than before-good) during all visits. Parents/caregivers who reported tics were asked whether these had changed in severity or specificity during the past week.

Based on direct interviews and parent reports, the investigator assessed the adverse events reported by parents/caregivers and the patients in terms of severity and relationship to OROS-MPH treatment. Severity was rated as "mild", "moderate", or "severe", and its relationship to OROS-MPH was rated as "probably related," "possibly related," or "not related."

Statistical Analysis

Differences in mean scores under the two medications, including changes in IOWA Conners scores compared with the baseline, were analyzed using paired t-tests. The effects of switching were also analyzed according to

Table 1. Clinico-demographic characteristics of subjects with ADHD

Variables	Children with ADHD (N=102)
Age (mean±standard deviation)	9.4±2.6
Sex (male : female)	94 : 8
Education and age span	N (%)
1 st -4 th elementary school (6-9 years)	81 (79.4%)
5 th -6 th elementary school (10-12 years)	14 (18.6%)
Junior high school (13-15 years)	2 (2%)
Comorbid conditions	N (%)
Any condition	35 (34.9%)
ODD	18 (17.6%)
Anxiety disorder	18 (17.6%)
Depression	10 (9.8%)
Conduct disorder	3 (2.9%)
Learning disorder	18 (17.6%)
Others	6 (5.9%)
ADHD subtype	N (%)
Inattentive type	24 (23.8%)
Hyperactive-impulsive type	6 (5.9%)
Combined type	72 (71.3%)
Pre-entry of study MPH-IR dose	N (%)
10-20 mg/day	55 (53.9%)
21-40 mg/day	39 (38.2%)
41-60 mg/day	8 (7.8%)

ADHD subtype. All subjects who received study medication were included in both the efficacy and safety analyses (i.e., intent-to-treat (ITT) population). All data analyses were performed using SPSS-PC version 11.0. Statistical significance was defined as P-values of 0.05 (two-tailed).

RESULTS

A total of 102 subjects were enrolled in the study and received study medication (the ITT population). Participants included children between the ages of 6 and 12 years (mean age: 9.4±2.6 years) with a DSM-IV diagnosis of ADHD (Table 1). Of the total sample, 72% were diagnosed with the combined type of ADHD, 23% with the inattentive type, and 5% with the hyperactive-impulsive type. Additionally, 34.9% of the patients had comorbid disorders: 18.6% had oppositional defiant disorder, 17.6% had anxiety disorders, and 17.6% had learning disorders. Of the 102 subjects, 97 (94.3%) completed the 28-day study.

Outcome and Efficacy Measures

Primary efficacy measure (Table 2)

After 28 days of OROS-MPH treatment, the effectiveness of this medication was evaluated primarily with the I/H subscale of the IOWA Conners scale. The ratings on

Table 2. Parent & Teacher IOWA Conners rating scale before and after OROS-MPH treatment

	Pre-tx (N=96)	Post-tx (N=96)	†
	Mean (S.D.)	Mean (S.D.)	
Parent IOWA			
Inattentive/Overactive	5.10 (2.45)	3.66 (2.27)	6.28***
Oppositional/Defiant	3.32 (2.29)	2.49 (2.05)	4.12***
Total	8.39 (4.18)	6.13 (4.01)	5.96***
Teacher IOWA			
Inattentive/Overactive	4.16 (2.98)	3.71 (2.76)	1.86
Oppositional/Defiant	2.72 (2.58)	2.47 (2.68)	1.34
Total	6.88 (5.02)	6.18 (5.15)	1.86

Pre-tx: pretreatment status, Post-tx: posttreatment status, S.D.: standard deviation, Statistically significant differences were found in paired t-test. *** $p < .001$.

the IOWA Conners I/H subscale completed by parents/caregivers and teachers are shown in Table 1. According to parent/caregiver ratings on the Conners I/H subscale, children with ADHD showed statistically significant improvement after 4 weeks of treatment with OROS-MPH ($t=6.28$, $p < .001$). However, the teachers' ratings on the same subscale did not reflect any significant improvement at the end of 4 weeks of treatment with OROS-MPH.

The subtype analysis showed statistically significant differences among subtypes in parent/caregiver ratings on the Conners I/H subscale ($p < 0.05$), but no differences were observed in the teacher ratings according to subtype.

Secondary efficacy measures (Table 2)

The ratings given by parents and teachers on the IOWA Conners O/D subscale are shown in Table 2. The parent ratings on the Conners O/D subscale indicated statistically significant improvement in children's behavior after 4 weeks of treatment with OROS-MPH ($t = 4.12$, $p < .001$). However, the Conners O/D subscales completed by teachers did not reflect any significant improvements. The subtype analysis showed significant differences in the parent ratings on the Conners O/D subscale according to subtype ($p < 0.05$), whereas no significant differences among subtypes were found in the teacher ratings.

The psychiatrists' ratings on the CGI scale (Table 2) indicated that 46.1% of children with ADHD were minimally improved, 27.5% were much improved, and 1.0% were very much improved after OROS-MPH treatment. Additionally, 3.9% of the children were rated as minimally worse, and 16.7% were rated as showing no change (Fig. 1).

Fig. 1. Clinician's rating on CGI-change after treatment of OROS-MPH (N=102). MW: Minimally worse, NC: No change, Minimal I: Minimally improved, Much I: Much improved, VMI: Very much improved.

Safety and Adverse Effects

All patients who received methylphenidate or OROS-MPH were included in the analysis of safety. No serious adverse events were reported during the study.

Appetite

At the end of MPH-IR treatment, 24.8% (25/101) of the children were reported as having a poor appetite, and 22.7% (22/97) were reported as having a poor appetite at the end of OROS-MPH treatment. This difference was not statistically significant.

Sleep

With MPH-IR, 8.9% (9/101) of subjects were assessed as having poor sleep, and 91.1% (93/101) were assessed as having fair to excellent sleep. At day 28 after OROS-MPH treatment, 8.2% (8/97) of children were reported as having poor sleep, and 91.8% of the subjects were assessed as having fair to excellent sleep. These changes were not statistically significant.

Tics

Before switching to OROS-MPH, 27.7% (28/101) of the children were reported as having mild to moderate tic symptoms. After receiving OROS-MPH for 28 days, 19.6% (19/97) were reported as having mild to moderate tic symptoms. This difference in the prevalence of tics observed before and after the switch was statistically significant. No subjects reached the criteria for Tourette's disorder during OROS-MPH treatment.

Comparison of frequency of adverse events

We examined mean differences between MPH-IR and OROS-MPH in terms of the frequency of adverse effects among children with ADHD. With OROS-MPH treatment, the children with ADHD showed fewer tics than with MPH ($t=2.57, p<.005$). We found no significant differences between the MPH- and OROS-MPH treatments children regarding sleep- and appetite-related side effects. The frequencies of adverse events relating to OROS-MPH (i.e., nausea, abdominal pain, headache, tics, anorexia, insomnia, and nervousness) were low, ranging from 1% to 7%, suggesting that OROS-MPH is a safe drug for treating children with ADHD.

DISCUSSION

This study was conducted to investigate the efficacy and tolerability of switching patients who had been stabilized on MPH-IR to an extended-release form of MPH (OROS-MPH). We also examined the effects of OROS-MPH via comparisons with standard b.i.d. or t.i.d. dosing regimens of MPH-IR. This study showed that MPH-IR could be successfully changed to OROS-MPH without any serious side effects. After OROS-MPH treatment, only about 4% of the study subjects were rated by psychiatrists as worse ("minimally worse") compared with when they were receiving MPH-IR treatment. The psychiatrists rated about 18% of the study subjects as unchanged compared with their status at baseline, and OROS-MPH treatment was rated by psychiatrists as superior to MPH-IR treatment for about 78% of the subjects.

Parents/caregivers reported better efficacy under the OROS-MPH treatment condition than under the MPH-IR condition according to ratings on the IOWA Conners I/H and O/D subscales. However, the teacher ratings reflected no significant changes after the switch from MPH-IR to OROS-MPH. Teachers also reported no significant improvement with OROS-MPH treatment compared with MPH-IR treatment with respect to peer interactions. Differences between parent/caregiver and teacher ratings seem to be attributable to the MPH-IR regimen. Prior to OROS-MPH treatment, 64% of the subjects had been on a b.i.d. regimen of MPH-IR; thus, the teachers would not have been expected to observe any significant differences between the two drug conditions given that their exposure to the children occurred when school was in session and the medication was still effective. However, because of its long span of action, OROS-MPH may have shown more persistent effects than MPH-IR, and these may have ex-

tended to the period after school.

The finding that OROS-MPH emerged as superior to MPH-IR b.i.d. on parent ratings indicated that the duration of action of OROS-MPH was sufficiently longer than that on the MPH-IR b.i.d. regimen. This result is very important not only for children with ADHD children but also for their parents. The difficulties that children with ADHD experience with completing homework and chores, complying with parental commands, and engaging in peer or sibling interactions may be improved with stimulants. Furthermore, problematic parent-child interactions and parental stress may also be ameliorated with stimulants.^{15,16} However, the increases in dosage after switching may also have contributed to the improvement observed after the OROS-MPH regimen was initiated. Because this study did not involve comparisons between individuals, we did not maintain strict dose-matching during the switching process.

Future research should examine how the present results relate to extant literature on the effects of MPH on children with ADHD. It is noteworthy that the medication had significant effects on parent-child relationships and on parent ratings on the IOWA O/D subscale in addition to its effects on ADHD symptoms. This finding is consistent with literature documenting that the effects of stimulants extended to a very important domain of concurrent impairments in children with ADHD: oppositional and defiant behavior as rated by the parents.¹⁷

Previous studies have generally shown that stimulants decreased rule violations, aggression, interruptions, and other ADHD-related behaviors that are bothersome to peers. In contrast, only one study has examined a small-group setting, and only one has examined a large-group unstructured setting.^{18,19} Because small groups constitute the majority of settings in which children (including children with ADHD) interact with peers and because interaction with peers in small groups (e.g., during board games) and in unstructured peer settings is clearly problematic for children with ADHD, the absence of information on the effects of stimulants during both small-group and recess activities represents a major gap in the literature. Data obtained by this study demonstrated that stimulant medication (both MPH-IR and OROS-MPH) had beneficial effects on decreasing negative peer interactions. We found no differences between the effectiveness of MPH-IR and of OROS-MPH according to teacher ratings of peer interactions. OROS-MPH has been shown to improve the behavioral and attentional symptoms of ADHD throughout a 12-h period,^{20,21} and its efficacy has

been shown to be comparable to that of t.i.d. MPH-IR in three short-term, randomized, controlled studies among children.^{20,21}

Side effects such as appetite loss, sleep disturbance, and tics were also evaluated, as were other adverse effects. No significant differences between the two drugs (MPH-IR: 24.8%, OROS-MPH: 22.7%) were noted related to appetite loss. Additionally, no significant differences between the two drugs (MPH-IR: 8.9%, OROS-MPH: 8.2%) were observed regarding sleep disturbances. Tic symptoms significantly decreased after switching from MPH-IR to OROS-MPH. With MPH-IR treatment, 27.7% (28/101) of subjects experienced tic symptoms compared with 19.6% (19/97) with OROS-MPH treatment, a statistically significant change. We do not know whether the reduction in tic symptoms resulted from switching to OROS-MPH or was the result of the natural course of tic symptoms.

This study has several limitations.

First, the switching process resulted in higher daily doses of MPH even though such differences were not large. Second, the groups who received b.i.d. vs. t.i.d. MPH-IR regimens were not separately compared after the switch to OROS-MPH. Third, investigators and participants were not blind to the treatment conditions. Thus, the ratings were subject to observer bias. Fourth, no control group was used.

Despite these limitations, the results of this study suggested that the MPH-IR regimen could be successfully changed to a once-daily OROS-MPH regimen without any serious adverse effects. This study also suggested that OROS-MPH was more consistently effective than MPH-IR for the control of behavioral symptoms.

■ Acknowledgments

This study was supported by Korean Jassen Pharmaceutical Company.

REFERENCES

1. Canino G, Shrout PE, Rubio-Stipec M, Bird HR, Bravo M, Ramirez R, et al. *The DSM-IV rates of child and adolescent disorders in Puerto Rico: prevalence, correlates, service use, and the effects of impairment.* Arch Gen Psychiatry 2004; 61:85-93.
2. Ford T, Goodman R, Meltzer H. *The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders.* J Am Acad Child Adolesc Psychiatry 2003;42:1203-1211.
3. Brown RT, Freeman WS, Perrin JM, Stein MT, Amler RW, Feldman HM, et al. *Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings.* Pediatrics 2001;107:E43.
4. Cho SC, Shin YO. *Prevalence of disruptive behavior disorder*

- ders. *J Korean Acad Child Adolesc Psychiatry* 1994;5:141-149.
5. Kim BN. Community based study for characteristics of children with subthreshold attention deficit hyperactivity disorder. *J Korean Neuropsychiatric Association* 2002;41:110-122.
  6. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American psychiatric Association; 1994.
  7. Goldman LS, Genel M, Bezman RJ, Slanetz PJ. *Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents*. Council on Scientific Affairs, American Medical Association. *JAMA* 1998;279:1100-1107.
  8. Steele M, Weiss M, Swanson J, et al. A randomized, controlled effectiveness trial of OROS-methylphenidate compared to usual care with immediate-release methylphenidate in attention deficit-hyperactivity disorder. *Can J Clin Pharmacol* 2006;13:50-62.
  9. Kim BN, Yoo HI, Kang HW, Shin DW, Ahn DH. The Korean practice parameter for the treatment of ADHD. *J Korean Acad Child Adolesc Psychiatry* 2007;18:10-31.
  10. Hwang JW, Kim BN, Cho SC. Compliance study of methylphenidate in the treatment of ADHD. *J Korean Acad Child Adolesc Psychiatry* 2004;15:160-167.
  11. Hinshaw SP, Melnick SM. Peer relationships in children with attention-deficit hyperactivity disorder with and without comorbid aggression. *Dev Psychopathol* 1995;7:627-647.
  12. Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, situational, and temporal effects of treatment of ADHD with methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1997;36:754-763.
  13. Remschmidt H, Hoare P, Ettrich C, Rothenberger A, Santosh P, Schmidt M, et al. Symptom control in children and adolescents with attention-deficit/hyperactivity disorder on switching from immediate-release MPH to OROS MPH. Results of a 3-week open-label study. *Eur Child Adolesc Psychiatry* 2005;14:297-304.
  14. Hoare P, Remschmidt H, Medori R, Ettrich C, Rothenberger A, Santosh P, et al. 12-month efficacy and safety of OROS MPH in children and adolescents with attention-deficit/hyperactivity disorder switched from MPH. *Eur Child Adolesc Psychiatry* 2005;14:305-309.
  15. Barkley RA, Cunningham CE. The effects of methylphenidate on the mother-child interactions of hyperactive children. *Arch Gen Psychiatry* 1979;36:201-208.
  16. Barkley RA, Karlsson J, Strzelecki E, Murphy JV. Effects of age and Ritalin dosage on the mother-child interactions of hyperactive children. *J Consult Clin Psychol* 1984;52:750-758.
  17. Pelham WE, Bender ME, Caddell J, Booth S, Moorer SH. Methylphenidate and children with attention deficit disorder. Dose effects on classroom academic and social behavior. *Arch Gen Psychiatry* 1985;42:948-952.
  18. Pelham WE Jr, McBurnett K, Harper GW, Milich R, Murphy DA, Clinton J, et al. Methylphenidate and baseball playing in ADHD children: who's on first? *J Consult Clin Psychol* 1990;58:130-133.
  19. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* 1999;56:1073-1086.
  20. Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 2001;107:E105.
  21. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. *Arch Gen Psychiatry* 2003;60:204-211.