

A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children With Attention-Deficit/Hyperactivity Disorder in the Laboratory School (The Comacs Study)

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ABSTRACT. *Objective.* The objective of this study was to evaluate differences in the pharmacodynamic (PD) profile of 2 second-generation extended-release (ER) formulations of methylphenidate (MPH): Metadate CD (MCD; methylphenidate HCl, US Pharmacopeia) extended-release capsules, CII, and Concerta (CON; methylphenidate HCl) extended-release tablets, CII. Little empirical information exists to help the clinician compare the PD effects of the available ER formulations on attention and behavior. Previous studies have shown that the near-equal doses of MCD and CON provide equivalent, total exposure to MPH as measured by area under the plasma concentration time curve, yet their pharmacokinetic (PK) plasma concentration versus time profiles are different. We previously offered a theoretical PK/PD account of the similarities and differences among available ER formulations based on the hypothesis that all formulations produce effects related to MPH delivered by 2 processes: 1) an initial bolus dose of immediate-release (IR) MPH that is expected to achieve peak plasma concentration in the early morning and have rapid onset of efficacy within 2 hours of dosing, which for the MCD capsule is delivered by 30% of the total daily dose as uncoated beads and for the CON tablet is delivered by an overcoat of 22% of the total daily dose; and 2) an extended, controlled delivery of ER MPH that is expected to achieve peak plasma concentrations in the afternoon to maintain efficacy for a programmed period of time after the peak of the initial bolus, which for the MCD capsule is delivered by polymer-coated beads and for the CON tablet by an osmotic-release oral system. According to this PK/PD model, clinical superiority is expected at any point in time for the formulation with the highest MPH plasma concentration.

Methods. This was a multisite, double-blind, double-dummy, 3-way crossover study of 2 active treatments (MCD and CON) and placebo (PLA). Children with confirmed diagnoses of attention-deficit/hyperactivity disorder were stratified to receive bioequivalent doses of MCD and CON that were considered to be low (20 mg of

MCD and 18 mg of CON), medium (40 mg of MCD and 36 mg of CON), or high (60 mg of MCD and 54 mg of CON), and in a randomized order each of the study treatments was administered once daily in the morning for 1 week. On the seventh day of each treatment week, children attended a laboratory school, where surrogate measures of response were obtained by using teacher ratings of attention and deportment and a record of permanent product of performance on a 10-minute math test at each of the 7 classroom sessions spread across the day at 1.5-hour intervals. Safety was assessed by patient reports of adverse events, parent ratings on a stimulant side-effects scale, and measurement of vital signs.

Results. The analyses of variance revealed large, statistically significant main effects for the within-subject factor of treatment for all 3 outcome measures (deportment, attention, and permanent product). The interactions of treatment \times session were also highly significant for all 3 outcome measures. Inspection of the PD profiles for the treatment \times session interactions suggested 4 patterns of efficacy across the day: 1) PLA > MCD ~ CON (PLA superiority) immediately after dosing; 2) MCD > CON > PLA during the morning (MCD superiority); 3) MCD ~ CON > PLA during the afternoon (PD equivalence of MCD and CON); and 4) CON > MCD ~ PLA in the early evening (CON superiority). The effect of site was significant, because some study centers had low and some high scores for behavior in the lab classroom, but both the low- and high-scoring sites showed similar PD patterns across the day. The interaction of dose \times treatment was not significant, indicating that the pattern of treatment effects was consistent across each dose level. There were no statistically significant overall differences among the 3 treatments for the frequency of treatment-emergent adverse events, ratings of side effects, or vital signs. Two additional PK/PD questions were addressed:

1. The a priori hypothesis called for a comparison of the average of sessions (removing session as a factor) during a time period that corresponds to the length of a typical school day (from 1.5 through 7.5 hours after dosing). For the planned contrast of the 2 treatment conditions (MCD versus CON), the difference was significant, confirming the a priori hypothesis of superiority of near-equal daily doses of MCD over CON for this predefined postdosing period.
2. In the design of the study, the dose factor represented the total daily dose, consisting of 2 components: the initial bolus doses of IR MPH, which differ for the near-equal total daily doses of MCD and CON, and the reservoir doses of ER MPH, which were the same for the 2 formulations. To evaluate the moderating

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effects of the bolus component of dose on outcome, average effect size (ES) was calculated for the efficacy outcomes at the time of expected peak PK concentration times of the initial bolus component for each formulation at the 3 dose levels. The correlation (r) of ES with IR MPH bolus dose was significant for each of the 3 outcome measures ($r \sim .9$), indicating that the magnitude of effects in the early morning may be attributed to the dose administered by the IR MPH bolus of each formulation. For the 2 dose conditions with equal 12-mg IR MPH boluses (MCD 40 and CON 54), the ESs were large and indistinguishable (eg, department ES ~ 0.75 for both).

Conclusions. Once-daily doses of MCD and CON produced statistically significantly different PD effects on surrogate measures of behavior and performance among children with attention-deficit/hyperactivity disorder in the laboratory school setting. As predicted by the PK/PD model, superiority at any point in time was achieved by the formulation with the highest expected plasma MPH concentration. *Pediatrics* 2004;113:e206–e216. URL: <http://www.pediatrics.org/cgi/content/full/113/3/e206>; ADHD, methylphenidate, pharmacodynamic effects, children, laboratory classroom, SKAMP, Metadate CD, Concerta.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; PD, pharmacodynamic; IR, immediate release; PK, pharmacokinetic; SR, sustained release; FDA, US Food and Drug Administration; ER, extended release; CON, Concerta; MCD, Metadate CD; TID, 3 times a day; BID, 2 times a day; AUC, plasma concentration time curve; PLA, placebo; SKAMP, Swanson, Kotkin, Atkins, M/Flynn, Pelham Scale; PERMP, permanent product; AE, adverse event; ANOVA, analysis of variance; ES, effect size; ITT, intent to treat.

Epidemiologic studies suggest that between 3% and 6% of the school-aged population in the United States meet the *Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition* criteria for attention-deficit/hyperactivity disorder (ADHD).¹ It is well established that ADHD symptoms typically emerge early in life and remain problematic in two thirds to three quarters of children in middle adolescence and that difficulties persist into late teenage years in academic and social domains.²

The use of methylphenidate (MPH) for the treatment of ADHD provides significant short-term symptomatic and classroom behavior improvement.³ The pharmacodynamic (PD) effects of immediate-release (IR) MPH match the pharmacokinetic (PK) profile of a given dose, with a maximum effect ~ 1.5 to 2.0 hours after dosing and a half-life of ~ 2.0 to 3.0 hours.^{4,5} Due to these PK and PD properties, multiple doses of IR MPH are usually required to maintain effectiveness across the day.⁶ The initial sustained-release (SR) formulations of MPH (eg, Ritalin SR), developed to overcome the need for multiple daily doses, were approved by the US Food and Drug Administration (FDA) for the treatment of ADHD decades ago, but they were not well accepted in clinical practice, apparently due to a perception of reduced clinical effectiveness, slower onset of action, and greater variability of response compared with IR MPH.⁷ Recently, second-generation, once-daily, extended-release (ER) formulations of MPH were de-

veloped that were shown to be as effective as multiple doses of IR MPH.^{8–10} After FDA approval, these new products^{11–14} were rapidly accepted into clinical practice.

Differences among the second-generation ER formulations of MPH exist; however, little empirical information is available to guide the selection of the most appropriate choice among the available new formulations for use in a particular clinical situation. A PK/PD model proposed by Swanson et al^{8,10} offers a theoretical account of the similarities and differences among these new ER formulations based on the hypothesis that all formulations produce effects related to the dose of MPH delivered by 2 processes: 1) an initial bolus delivery of IR MPH that is expected to achieve peak plasma concentrations in the early morning and have rapid onset of efficacy within 2 hours of dosing and 2) an extended, controlled delivery of ER MPH that is expected to achieve higher plasma concentrations in the afternoon than in the morning to maintain efficacy for a programmed period of time after the peak of the initial bolus. According to this PK/PD model, clinical superiority at any point in time would be expected for the ER MPH formulation with the highest MPH plasma concentration.

The objective of the current study was to compare the clinical effect of 2 second-generation ER formulations of MPH: Concerta (CON) and Metadate CD (MCD). CON was designed to replace 3-times-a-day (TID) regimens of IR MPH and consists of an insoluble OROS tablet formulation with 22% of the dose in an IR overcoat and 78% in a controlled-release bilayer core inside a membrane, which also contains a water-sensitive polymer that expands and results in drug delivery by an osmotic process.^{8,13} MCD was designed to replace 2-times-a-day (BID) regimens of IR MPH and consists of a capsule formulation containing 30% of the dose in IR MPH beads and 70% of the dose in ER MPH beads coated with a controlled-release polymer to deliver MPH gradually over a 12-hour time frame.^{9,14} Both CON¹¹ and MCD¹² have been shown individually in randomized, controlled clinical trials to be safe and effective for the treatment of ADHD in school-aged children, and both are available in near-equal daily doses considered to be in the low (20 mg of MCD and 18 mg of CON), medium (40 mg of MCD and 36 mg of CON), and high (60 mg of MCD and 54 mg of CON) ranges of clinical doses of MPH.

These near-equal daily doses of MCD and CON were compared recently in a crossover study in healthy adult volunteers.¹⁵ When compared for total exposure to MPH, measured as area under the plasma concentration time curve (AUC), and maximum plasma concentration (C_{max}), the dose pairs met current FDA criteria for single-dose bioequivalence. However, despite these similarities, the plasma concentration versus time profiles produced by these 2 formulations were shown to be clearly different: Plasma concentrations of MPH were significantly higher for MCD than for CON for up to 6 hours after dosing, and by contrast, plasma concentrations of MPH were significantly higher for CON at

8, 10, and 12 hours after dosing. These differences can be ascribed to differences in the formulation of the products that affect both the amount and the timing of release of both the IR and ER components. For example, MCD releases 50% more IR MPH in the initial bolus delivery process than CON (6 vs 4 mg at the low daily dose, 12 vs 8 mg at the medium daily dose, and 18 vs 12 mg at the high daily dose) but the same amount of ER MPH (for both MCD and CON, 14 mg at the low, 28 mg at the medium, or 42 mg at the high daily doses).

We adopted a nonequivalence design for a direct (head-to-head) comparison of the PD effects of MCD and CON administered at bioequivalent daily doses. The use of a nonequivalence comparison is controversial; therefore, an inactive (placebo [PLA]) condition was included to allow comparisons with the literature on efficacy and safety of the respective MPH formulations. We used the University of California at Irvine Laboratory School Protocol¹⁶ to control for timing and context of assessment across the day and used surrogate measures of efficacy to evaluate the comparative efficacy of MCD and CON at specific time points across the entire day in the laboratory school. We performed a full analysis of the main effects of the study that are relevant to the PD response (dose: low, medium, and high; treatment: MCD, CON, and PLA; time: 7 sessions) as well as their interaction (dose × treatment × time). In addition, we tested an a priori hypothesis that provided the rationale for the study to evaluate the average effects measured over a specified period (1.5- to 7.5-hour postdosing) corresponding to the typical school day.

METHODS

Clinical Materials

MCD 20-mg capsules (lot CL-02088) were obtained from Euran Americas, Inc (Vandalia, OH). CON tablets (18, 36, and 54 mg; lots 0116991, 0111487, and 0116969, respectively) were obtained from Alza Corporation (Mountain View, CA) and overencapsulated in size-0 hard-gelatin capsules by PCI Clinical Services (Philadelphia, PA). The resulting overencapsulated CON tablets were tested according to the US Pharmacopeia dissolution conditions for MPH tablets. A statistical F2 comparison of the dose fraction in solution at each sampling time point showed a comparable dissolution profile to unencapsulated CON tablets from the same commercial lot (F2 > 70 for all doses), indicating no significant effect of overencapsulation on the in vitro release of MPH (Celltech Pharmaceuticals Inc, unpublished data, 2002). PLAs for MCD and overencapsulated CON were manufactured by PCI Clinical Services.

Treatments were packaged according to a double-dummy design. Each treatment pack contained a 1-week supply of study treatment, with each day's supply consisting of 1 large capsule to

accommodate the size of any dose level of CON (containing CON or PLA) and, depending on dose level, between 1 and 3 smaller MCD-sized capsules (containing MCD or PLA).

Patients

Children (6–12 years old) were recruited who had clinical diagnoses of a *Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition* subtype of ADHD (inattentive type, hyperactive-impulsive type, or combined type) and were being treated with MPH in doses of 10 to 60 mg/day (5–20 mg per administration, 1–3 times a day). The physician at each center chose his/her own patient-recruitment method (ie, chart review or advertisement). The clinical diagnosis of ADHD was confirmed by a structured parent interview using the National Institute of Mental Health Diagnostic Interview Schedule for Children (version 4.0). Children were deemed otherwise healthy by means of a medical history, physical examination, vital-sign measurements (blood pressure, heart rate, respiration, and temperature), and clinical laboratory assessments (hematology and urinalysis). In addition, children had to demonstrate the ability to swallow PLA study-treatment capsules whole and without difficulty.

Exclusion criteria included an intelligence quotient <80 or the inability to follow or understand study instructions; pregnancy; a history of seizure or tic disorder; a family history of seizure or Gilles de La Tourette's syndrome; congenital cardiac abnormality, a history of cardiac disease including myocardial infarction within 3 months of study entry, glaucoma, or hyperthyroidism; a history of substance abuse or a caretaker with a history of substance abuse; concurrent chronic or acute illness or other condition that might confound the study rating measures; a documented allergy or intolerance to MPH; the use of an investigational drug within 30 days of study entry; and the use of concomitant medication that could interfere with the assessment of efficacy and safety of the study treatments. Children provided signed assent, and their legal guardians signed an institutional review board–approved consent form to participate in the study.

Study Design

This was a double-blind, PLA-controlled, crossover study comparing 3 treatment conditions: MCD, CON, and PLA. The study was conducted at 10 centers in the United States in accordance with the principle of the Declaration of Helsinki and its amendments and the International Committee on Harmonization E6 guidelines on Good Clinical Practice. The study protocol and assent and consent forms were approved by the institutional review board for each study site before initiation of the study.

Eligible patients were assigned to a dose level according to their preexisting dosing requirement for MPH (see Table 1) and remained at this level for the study duration. Children treated with low doses (≤20 mg/day) of MPH were randomized to receive MCD 20, CON 18, or PLA; those treated with medium doses (>20 to 40 mg/day) were randomized to receive MCD 40, CON 36, or PLA; and children treated with high doses (>40 mg/day) were randomized to receive MCD 60, CON 54, or PLA. Within each stratum, patients were assigned to 1 of the 6 treatment sequences of MCD, CON, and PLA to balance for the order of administration of the treatments. Each of the 3 treatments was administered for 7 days (in the assigned sequence) without an intervening washout period.

The Laboratory School

The patients were assessed in the laboratory school on days 7, 14, and 21. The standard laboratory classroom staff included a

TABLE 1. Dosage Stratification

Previous MPH Daily Dose	Stratification Dose
Low dose ≤15 mg of IR MPH or ≤20 mg of ER MPH (eg, 5 mg BID/TID or 20 mg of MPH SR)	MCD 20 mg vs CON 18 mg vs PLA (dose level 1)
Medium dose >10 to ≤30 mg IR MPH or >20 to ≤40 mg of ER MPH (eg, 10 mg BID/TID or 40 mg of MPH SR)	MCD 40 mg vs CON 36 mg vs PLA (dose level 2)
High dose >30 mg IR MPH or >40 mg of ER MPH (to a maximum of 60 mg) (eg, 15 mg BID/TID or 60 mg of MPH SR)	MCD 60 mg vs CON 54 mg vs PLA (dose level 3)

TABLE 2. Daily Schedule of Assessments During Laboratory Classroom Day

Study Hour*	Preparation	-0.75	0 (Dose)	1.5	3.0	4.5	6.0	7.5	9	12
Time		[6:45 AM]	[7:30 AM]	[9:00 AM]	[10:30 AM]	[12:00 PM]	[1:30 PM]	[3:00 PM]	[4:30 PM]	[7:30 PM]
Vital signs†		X		X	X	X	X	X	X	X
SKAMP deportment			X	X	X	X	X	X		X
SKAMP attention			X	X	X	X	X	X		X
PERMP			X	X	X	X	X	X		X
Complete Barkley Scale (parent/guardian)	X									
Assess AEs	X									

* The chronological (clock) time was ± 15 minutes this time, but the time between assessments was 1.5 hours.

† The subject's temperature was obtained only during the initial vital-signs collection for the day.

clinical teacher, an activity teacher, and 2 trained observers to rate each child, but adjustments were made depending on the number of students in a classroom (from 4 to 18). In addition, playground counselors and medical staff supervised nonclassroom activities, which included recording of vital signs and participation in group games in a playground or gym.

The laboratory school days lasted for ~ 13 hours and included 7 sessions: 1 preparation classroom period immediately after dosing, 5 classroom periods separated by 1.5-hour intervals across the typical school day, and 1 classroom period 4.5 hours later at the end of the day. A 1.5-hour cycle of activities was used to control for timing and setting of the assessments as prescribed by in the University of California at Irvine Laboratory School Protocol (see Table 2).¹⁶ The 2 trained observers assessed subjects during each classroom session on the Swanson, Kotkin, Atkins, M/Flynn, Pelham Scale (SKAMP),¹⁷ consisting of 6 deportment items (interacting with other children, interacting with adults, remaining quiet, staying seated, complying with the teacher's directions, and following the classroom rules) and 7 attention items (getting started, sticking with tasks, attending to an activity, making activity transitions, completing assigned tasks, performing work accurately, and being neat and careful while writing or drawing). In addition, during each classroom session, a written 10-minute math test was administered to provide an objective measure from its permanent product (PERMP), defined as the number of problems answered correctly.¹⁸

The outcome measures obtained at each of the 7 classroom periods were intended to document differences in the PD profiles of the 3 treatments (MCD, CON, and PLA) that were predicted by the PK/PD model.¹⁰ The first session (at time 0) was scheduled to occur before the bolus dose of IR MPH delivered by MCD or by CON was absorbed and thus before it was expected to produce an effect. The following 3 sessions before lunch (1.5, 3.0, and 4.5 hours after dosing) were scheduled when the larger bolus dose delivered by MCD (via IR MPH beads) and the greater proportion of ER MPH delivered during this time (via ER MPH beads) were expected to produce higher plasma concentrations than the bolus dose delivered by CON (via the IR MPH overcoat) and the ER MPH delivered by CON. The next 2 sessions after lunch (6.0 and 7.5 hours after dosing) were scheduled to occur during the school day afternoon when the combinations of IR and ER MPH deliveries by MCD and CON were expected to yield approximately the same plasma concentrations. The last session was delayed until 12.0 hours after dosing and scheduled in the early evening when the ER component of CON was expected to produce higher plasma concentrations than the ER component of MCD.

Safety

Safety was assessed by adverse event (AE) reports by the patient, parent, or guardian. The reported AEs were characterized (by the investigator at each site) as mild, moderate, or severe: a mild AE would require minimal or no treatment; a moderate AE would result in a low level of inconvenience or concern; and a severe AE would interrupt a patient's usual daily activity and may require drug or other therapy. In addition, each week, the parent or guardian completed the Barkley Side Effect Rating Scale,¹⁹ which delineates 17 side effects commonly reported during treatment with stimulant medication. The parent/guardian assessed the presence and severity of these side effects during the past week, rating each item on a scale of 0 (absent) to 9 (severe). The

children's temperatures were measured at the start of each classroom day, and blood pressure and heart rate were measured before or after each classroom session.

Statistical Analyses

For factorial analyses, the SAS analysis of variance (ANOVA) program for the General Linear Model was used. A mixed model was specified to perform a standard evaluation of 2 within-subject factors (treatment and session) and 3 between-subject factors (dose, site, and sequence) and their interactions. Not all sequences were assigned to each of the combinations of site and dose, so interactions of sequence with site and dose were not included in the ANOVA model. For the PD analyses described here, we selected the SAS General Linear Model option that utilizes data from just those subjects with complete data (ie, those cases without missing data). To maintain an overall significance level at $P < .05$ across the 3 outcome measures, a Bonferroni correction for multiple tests was made, and a P value $< .016$ for any individual outcome measure was required for significance.²⁰

We evaluated multiple comparisons of the 3 treatments by estimating effect sizes (ESs), which were calculated by dividing the difference between the active treatment mean and the PLA treatment means by the square root of the mean square error term from the ANOVA (ie, the pooled estimate of the standard deviation). We also compared treatments by using paired sample t tests.

In addition, we evaluated an a priori hypotheses about treatment effects averaged over the laboratory classroom sessions occurring during the typical school day (the 5 classroom sessions occurring from 1.5 to 7.5 hours after dosing) and compared treatments by using paired sample t tests. For the nonequivalence design, the sample size to achieve statistical power (> 0.9) was set based on this a priori hypothesis of an expected small difference (an ES of ~ 0.225) between MCD and CON on a single outcome measure (the average ratings of deportment).

RESULTS

Subjects

A total of 214 patients were screened for participation into the study, and 184 patients were stratified across the 3 dose levels based on their previously established clinical doses of MPH. Table 3 summarizes patient demographic information for the intent-to-treat (ITT) sample. Most of the patients met the criteria for ADHD combined type. Approximately 25% had a comorbid condition; anxiety and oppositional defiant disorder were the most frequently reported comorbidities. At prescreening, $\sim 91\%$ of the patients were on once-a-day dosing regimens; of the remainder, 7.6% were taking IR MPH BID, and 1.6% were taking IR MPH TID. In addition, 1.0% of patients were taking *d*-MPH (Focalin). Of the 184 subjects entering the study, 157 received all 3 levels of treatment and participated in all 7 classroom sessions. Of these subjects, the number at the 10 sites varied (at sites 1–10, $n = 4, 13, 6, 4, 7, 24, 10, 26, 26,$

TABLE 3. Summary of Demographics by All Treatments (ITT)

	Treatment Group		
	MCD (N = 174)	CON (N = 181)	PLA (N = 183)
Age, mean (SD)	9.7 (1.8)	9.6 (1.8)	9.6 (1.8)
Gender, n (%)			
Male	128 (73.6)	134 (74.0)	135 (73.8)
Female	46 (26.4)	47 (26.0)	48 (26.4)
Race, n (%)			
White	121 (69.5)	124 (68.5)	126 (69.2)
African American	20 (11.5)	21 (11.6)	21 (11.5)
Asian	3 (1.7)	3 (1.7)	3 (1.6)
Hispanic	21 (12.1)	23 (12.7)	23 (12.6)
Other	9 (5.2)	10 (5.5)	10 (5.5)
Subtype of ADHD, n (%)			
Inattentive	23 (13.2)	23 (12.7)	24 (13.1)
Hyperactive/impulsive	8 (4.6)	9 (5.0)	9 (4.9)
Combined	143 (82.2)	149 (82.3)	150 (82.0)

SD indicates standard deviation.

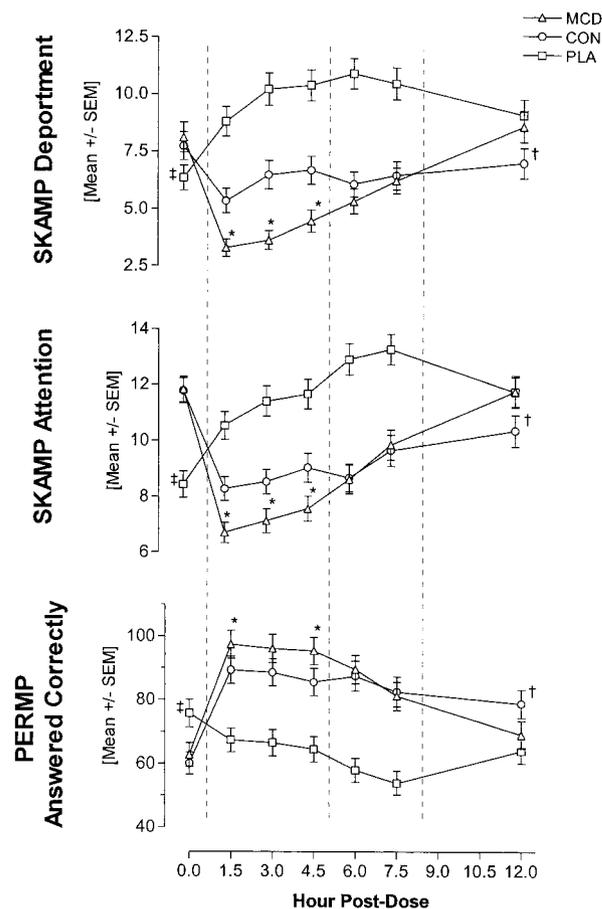
and 37, respectively), as did the number in the 3-dose strata (at doses 1–3, $n = 57, 53,$ and $47,$ respectively). The demographic characteristics of the sample of patients that completed all 3 treatments ($n = 157$) were not different than those reported for the full sample.

Overall ANOVAs

The overall ANOVAs revealed large main effects for all 3 outcome measures for the within-subject factors of treatment (department: $F[2, 260] = 64.41, P < .0001$; attention: $F[2, 260] = 26.50, P < .0001$; PERMP: $F[2, 260] = 21.84, P < .0001$) and session (department: $F[6, 780] = 16.75, P < .0001$; attention: $F[6, 780] = 27.76, P < .0001$; PERMP: $F[6, 780] = 25.11, P < .0001$). The interaction of treatment \times session was also highly significant for all 3 outcome measures (department: $F[12, 1560] = 20.02, P < .0001$; attention: $F[12, 1560] = 20.40, P < .0001$; PERMP: $F[12, 1560] = 16.94, P < .0001$).

These significant interactions suggest that the treatments differed but the pattern depended on the time of the assessment (ie, the session) and called for a simple-effect analysis of the treatments effects at each of the 7 assessment times separately. As shown in Fig 1, this revealed 4 general patterns of treatment efficacy that were consistent across the 3 measures: 1) immediately after dosing, the PLA treatment was better than either active treatment; 2) during the morning when MCD was better than CON and both active treatments were better than PLA; 3) during the afternoon when MCD and CON were, for the most part, similar in efficacy, but both active treatments were still superior to PLA; and 4) in the early evening when CON but not MCD was superior to PLA in some measures. ES estimates for MCD and CON at each session for each of the 3 outcome measures are shown in Fig 1. For each outcome measure, the maximum ES occurred during the morning sessions for MCD and during the afternoon sessions for CON.

The between-subject factor of dose was significant for SKAMP attention ($F[2, 130] = 5.10, P = .0074$) but not for SKAMP department ($F[2, 130] = 1.54, P = .2191$) or PERMP ($F[2, 130] = 4.16, P = .0178$). The



	Effect Size at Each Hour Post-Dose						
	0.0	1.5	3.0	4.5	6.0	7.5	12
SKAMP Department							
MCD	-.23	.82	.89	.80	.76	.54	.06
CON	-.18	.52	.50	.50	.66	.51	.25
SKAMP Attention							
MCD	-.59	.70	.72	.66	.65	.50	.00
CON	-.58	.41	.48	.42	.64	.53	.20
PERMP # Correct							
MCD	-.27	.57	.56	.59	.58	.50	.10
CON	-.33	.42	.42	.40	.54	.53	.28

Fig 1. SKAMP department, SKAMP attention, and PERMP scores over time after treatment with MCD (Δ), CON (\circ), or PLA (\square). The data represent the mean \pm standard error of the mean for all dose levels combined. Both MCD and CON were statistically significantly better than PLA at hours 1.5–7.5 for all 3 assessments ($P < .016$). Asterisks indicate the times at which MCD was statistically significantly better than CON; daggers, the times at which CON was statistically significantly better than MCD and PLA; double daggers, the times at which PLA was statistically significantly better than both MCD and CON. The corresponding ESs for MCD and CON at each session are shown in the table.

interaction of dose \times treatment was not significant at $P < .016$ for any of the 3 outcome measures.

The between-subject factor of site was highly significant ($P < .001$) for all 3 outcome measures (department: $F[9, 130] = 9.32$; attention: $F[9, 130] = 14.93$; PERMP: $F[9, 130] = 3.55$), and for the 2 subjective outcome measures from the SKAMP, the site \times treatment \times session interactions were also significant (department: $F[108, 1560] = 2.19, P < .0001$; attention: $F[108, 1560] = 1.34, P < .0126$). These significant interactions complicate the interpretation of the overall treatment main effects and the treatment \times session interaction effects (described above) and called for analyses of simple effects.

TABLE 4. ES Estimates for the Low- and High-Scoring Sites

	ES at Each Hour Postdose						
	0	1.5	3.0	4.5	6	7.5	12
High-scoring sites							
SKAMP deportment							
MCD	-0.33	1.2	1.3	1.0	1.0	0.64	0.12
CON	-0.26	0.82	0.75	0.67	0.87	0.62	0.41
SKAMP attention							
MCD	-0.67	0.87	0.90	0.66	0.84	0.38	0.13
CON	-0.62	0.55	0.60	0.38	0.83	0.48	0.11
PERMP (no. correct)							
MCD	-0.31	0.62	0.62	0.54	0.61	0.40	-0.02
CON	-0.35	0.51	0.42	0.39	0.54	0.49	0.22
Low-scoring sites							
SKAMP deportment							
MCD	-0.19	0.56	0.63	0.71	0.69	0.61	0.01
CON	-0.14	0.30	0.37	0.42	0.61	0.56	0.18
SKAMP attention							
MCD	-0.62	0.60	0.64	0.76	0.59	0.73	0.13
CON	-0.65	0.32	0.44	0.53	0.59	0.70	0.36
PERMP (no. correct)							
MCD	-0.23	0.54	0.49	0.65	0.56	0.61	0.21
CON	-0.31	0.34	0.42	0.42	0.55	0.57	0.34

Simple-Effect ANOVAs

Inspection of main effects revealed low ratings for SKAMP deportment and ATTENTION at 3 sites, with average ratings per item <1.0. For the posthoc simple-effects analysis, we grouped the sites into "low-scoring sites" ($n = 87$) and "high-scoring sites" ($n = 70$) subgroups and analyzed them in separate ANOVAs to determine how this characteristic of site moderated effects of treatment. In the simple-effects analyses, the between-subject factor of site was significant for all 3 outcome measures, but the site \times treatment interactions were not significant for any of the 3 measures in the analyses of either the high- and low-scoring subgroups, indicating that the treatment effect was consistent despite the difference in the overall ratings of these subgroups of sites. In separate analyses of these subgroups, the effect of treatment remained significant in both the high-scoring (deportment: $F[2, 92] = 30.96, P < .0001$; attention: $F[2, 92] = 12.61, P < .0001$; PERMP: $F[2, 92] = 9.94, P < .0001$) and low-scoring (deportment: $F[2, 134] = 25.90, P < .0001$; attention: $F[2, 134] = 31.65, P < .0001$; PERMP: $F[2, 134] = 23.43, P < .0001$) subgroups. Also, session remained significant in both the high-scoring (deportment: $F[6, 276] = 10.18, P < .0001$; attention: $F[6, 276] = 22.04, P < .0001$; PERMP: $F[6, 276] = 16.48, P < .0001$) and low-scoring (deportment: $F[6, 402] = 3.71, P = .0013$; attention: $F[6, 402] = 8.74, P < .0001$; PERMP: $F[6, 402] = 13.28, P < .0001$) subgroups. Finally, the interaction of treatment \times session also remained significant for the high-scoring (deportment: $F[12, 552] = 10.58, P < .0001$; attention: $F[12, 552] = 11.62, P < .0001$; PERMP: $F[12, 552] = 9.79, P < .0001$) and low-scoring (deportment: $F[12, 804] = 8.17, P < .0001$; attention: $F[12, 804] = 15.61, P < .0001$; PERMP: $F[12, 804] = 10.66, P < .0001$) subgroups. As shown in Table 4, the low-scoring subgroup showed smaller treatment effects than the high-scoring subgroup, and the inclusion of the low-scoring subgroup (with unexpected low ratings in the laboratory classroom set-

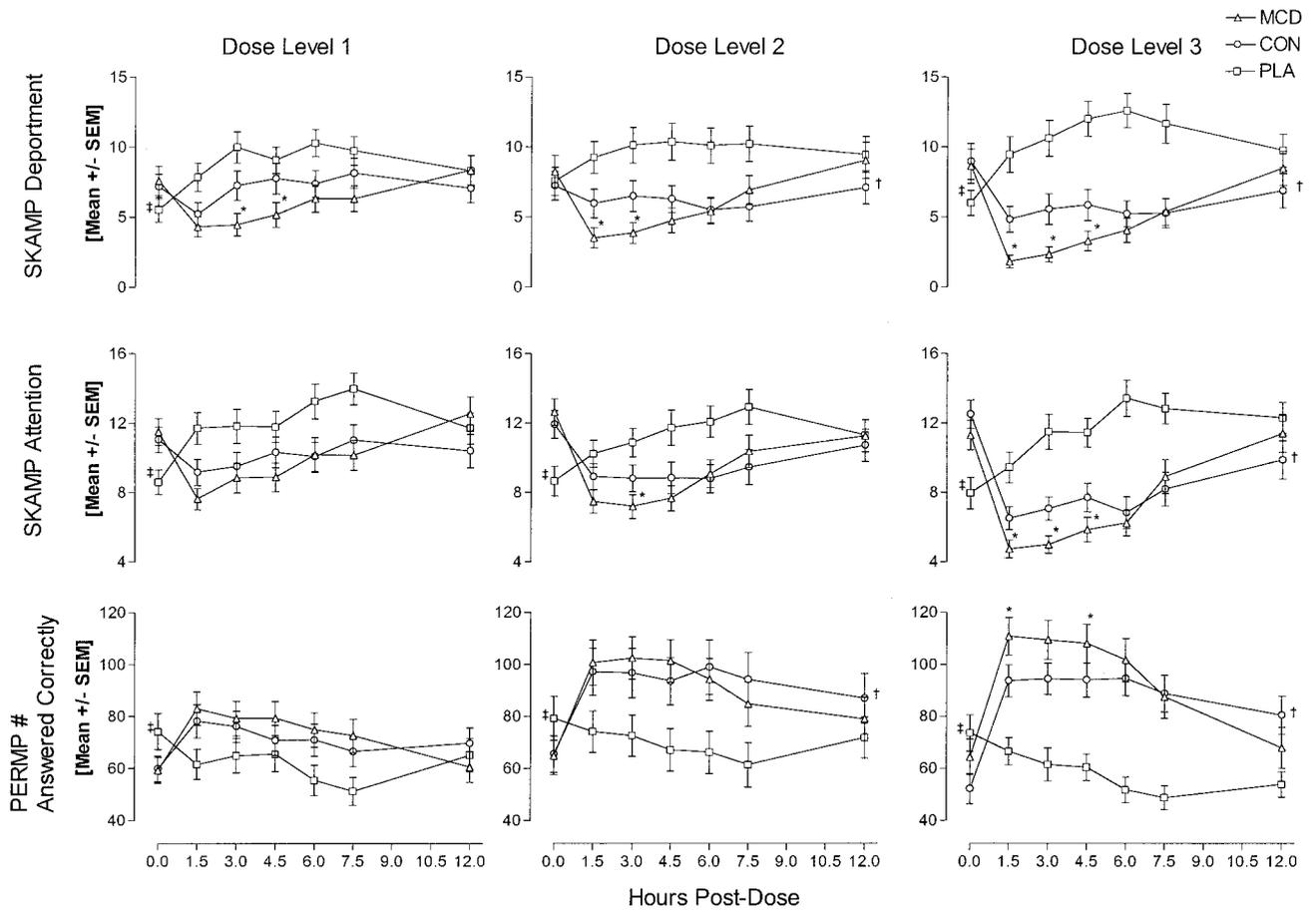
ting) attenuates but does not contradict the overall analyses.

In the overall analyses, the dose \times treatment interactions were not significant at $P < .016$ (our established significance level with a Bonferroni correction for multiple tests), but the dose \times treatment interactions were significant at the unadjusted significance level of $P < .05$ for attention ($F[4, 260] = 2.46, P = .0460$) and PERMP ($F[4, 260] = 3.08, P = .0168$). Based on this trend, we performed the simple-effects analyses separately for the 3 dose levels, which revealed that the same patterns of treatment effects were present in each of the subgroups stratified by clinical dose (see Fig 2).

In the design of the study, the dose factor refers to the total daily dose, consisting of 2 components that were described earlier (ie, the initial bolus doses of IR MPH, which differ for the near-equal total daily doses of MCD and CON, and the reservoir doses of ER MPH, which were the same for the 2 formulations). To evaluate the moderating effects of the bolus dose on outcome, we related the size of the drug effects (ESs) to the initial bolus components of each formulation at the 3 dose stratifications (low: CON 18 = 4 mg and MCD 20 = 6 mg; medium: CON 36 = 8 mg, MCD 40 = 12 mg; high: CON 54 = 12 mg and MCD 60 = 18 mg). Because the initial bolus dominates the PK levels at 1.5 and 3.0 hours after dosing, we calculated a correlation of the average ES at these 2 times with IR MPH bolus dose. As shown in Fig 3, the correlations were high and significant for all 3 outcome measures (deportment: 0.932; attention: 0.865; PERMP: 0.912), indicating that despite the selection of dose based on clinical titration, the ESs obtained in the early morning were directly related to the absolute dose administered in the IR MPH bolus of each formulation (ie, the dose delivered by the IR beads of MCD and by the overcoat of CON).

Test of the "a Priori" Hypothesis

To test the a priori hypothesis, for each subject a summary score was established for the primary outcome measure (SKAMP deportment) based on the sessions during a time period corresponding to the length of a typical school day (ie, sessions 2–6, which occurred from 1.5 through 7.5 hours after dosing). This averaging process removes session as a factor, and thus it does not evaluate the time course. This process increases the precision of measurement for a priori or posthoc tests,^{21,22} and similar strategies have been used to investigate differences between 2 active treatments that may be small but clinically meaningful.^{23,24} An ANOVA of the summary outcome measure revealed a significant main effect of treatment ($F[2, 162] = 64.07, P < .0001$) as well as site ($F[9, 81] = 7.68, P < .0001$) and site \times treatment ($F[18, 162] = 2.97, P = .0001$). For the planned contrast of the 2 treatment conditions (MCD versus CON) on SKAMP deportment, the difference was significant (mean difference = 1.62, $t[156] = 5.33, P < .0001$), confirming the a priori hypothesis of superiority of near-equal daily doses of MCD over CON for this postdosing period. In ANOVAs of the summary



	0.0	1.5	3.0	4.5	6.0	7.5	12
SKAMP Department							
MCD	-.29	.54	.73	.53	.55	.45	-.01
CON	-.23	.40	.36	.18	.40	.21	.16
SKAMP Attention							
MCD	-.51	.70	.45	.44	.43	.57	-.12
CON	-.43	.44	.35	.22	.44	.44	.18
PERMP #Correct							
MCD	-.34	.46	.29	.29	.41	.48	.10
CON	-.33	.35	.23	.11	.33	.35	.10

	0.0	1.5	3.0	4.5	6.0	7.5	12
SKAMP Department							
MCD	-.09	.81	.81	.72	.62	.41	.04
CON	.04	.46	.47	.52	.60	.55	.26
SKAMP Attention							
MCD	-.68	.52	.66	.63	.49	.36	.01
CON	-.55	.25	.37	.45	.53	.49	.09
PERMP #Correct							
MCD	-.26	.42	.48	.55	.43	.35	.11
CON	-.25	.37	.39	.43	.50	.49	.24

	0.0	1.5	3.0	4.5	6.0	7.5	12
SKAMP Department							
MCD	-.33	1.2	1.2	1.2	1.2	.80	.15
CON	-.38	.72	.73	.87	1.1	.81	.34
SKAMP Attention							
MCD	-.57	.97	1.3	1.0	1.2	.60	.13
CON	-.78	.60	.86	.69	1.1	.72	.35
PERMP #Correct							
MCD	-.21	1.0	1.0	1.1	1.1	.82	.30
CON	-.43	.63	.72	.76	.92	.85	.57

Fig 2. SKAMP department, SKAMP attention, and PERMP scores over time after treatment with MCD (Δ), CON (\circ), or PLA (\square) for the 3 dose levels. Both MCD and CON were statistically significantly better than PLA at hours 1.5–7.5 for all 3 assessments independent of dose level ($P < .016$), with the exception of CON at the 4.5- and 7.5-hour assessment times for SKAMP department and the 3.0- and 4.5-hour assessment times for PERMP at dose level 1 and the 1.5- and 4.5-hour assessment times for SKAMP attention at dose levels 2 and 1, respectively. Asterisks indicate the times at which MCD was statistically significantly better than CON; daggers, the times at which CON was statistically significantly better than PLA; double daggers, the times at which PLA was statistically significantly better than both MCD and CON, with the exception of dose-level-1 SKAMP department ratings and dose-level-3 PERMP ratings at which PLA was statistically better than CON only and dose-level-1 and -2 PERMP ratings at which PLA was statistically better than MCD only. The corresponding ESs for MCD and CON for each session within each dose level are shown in the tables.

scores for the secondary outcome measures, the main effect of treatment was also significant for SKAMP attention ($F[2, 162] = 35.57, P < .0001$) and PERMP ($F[2, 162] = 22.76, P < .0001$). In these secondary analyses, the main effect of site was also significant (SKAMP attention: $F[9, 81] = 9.43, P < .0001$; PERMP: $F[9, 81] = 3.41, P = .0013$), but the site \times treatment interactions were not. Pairwise comparisons revealed that treatment with MCD resulted in statistically significantly lower SKAMP attention ratings (mean difference = 0.86, $t[156] = 3.70, P = .0003$), whereas PERMP scores were not statistically different at $P < .016$ (mean difference = 5.22, $t[156] = 2.22, P = .0275$).

Safety and Tolerability Outcomes

There was no difference for any comparison of treatment groups on parent ratings of side effects on the Barkley Scale. In the ANOVA of the measures of blood pressure and pulse rate, only 2 statistically significant differences related to treatment emerged: 1) systolic blood pressure at hour 7.5 had a mean increase from baseline of 5.2 mm Hg for CON and 0.9 mm Hg for PLA and a decrease of 0.6 mm Hg for MCD ($P = .0075$), and 2) the mean increase from baseline at hour 1.5 for the pulse rate was 9.6 beats per minute for MCD, 9.5 beats per minute for CON, and 3.2 beats per minute for PLA ($P = .0244$). There was no significant difference due to the between-

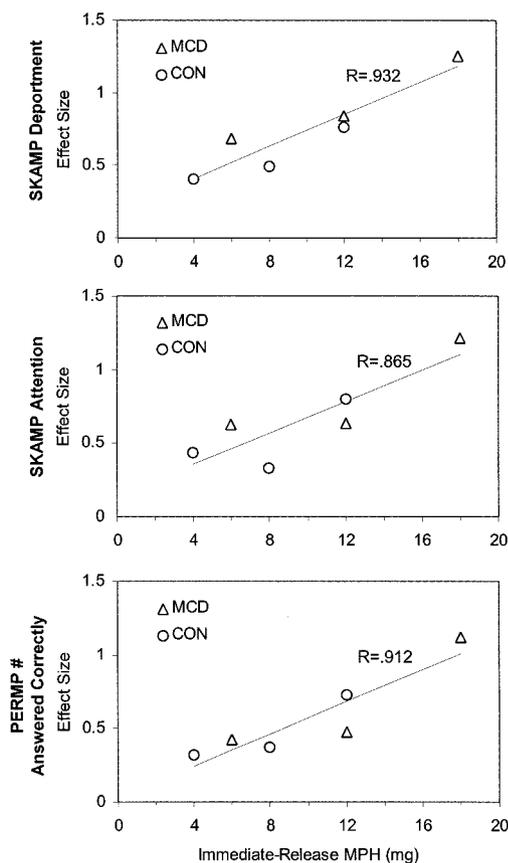


Fig 3. ESs for SKAMP department, SKAMP attention, and PERMP scores at hours 1.5 and 3.0 as a function of IR MPH in each formulation after treatment with MCD (Δ) and CON (\circ).

subject effect of dose. These findings are consistent with other observations of a slight increase in pulse rate and blood pressure fluctuations with clinical doses of MPH.²⁵

No severe AEs occurred. Less than one fourth of the patients in any treatment group experienced AEs, and of these AEs, most were mild. Three patients discontinued study treatment due to AEs that were judged to be unrelated to the medications. The reasons for discontinuation of treatment were gastroenteritis (CON), fever on classroom day (PLA), and sunburn (PLA). Table 5 displays the most frequent AEs categorized by body system that occurred in $\geq 2\%$ of the study sample. Upper abdominal pain was the most common AE for patients treated with MCD (3.4%) and CON (4.4%). A higher incidence of anorexia was seen with the active treatments (2.9% for MCD, 2.8% for CON) compared with PLA (1.1%), whereas a higher incidence of vomiting, insomnia, and irritability was seen with PLA (2.2%, 3.3%, and 2.7%, respectively), compared with MCD (0.6%, 1.7%, and 1.7%, respectively) and CON (0.6%, 1.7%, and 1.1%, respectively). Overall, the incidence of specific AEs was low and similar to those reported previously for MPH¹⁹

DISCUSSION

The current study examined whether the differences in expected PK profiles for MCD and CON produce differences in the time course of behavioral

effects as predicted by the PK/PD model used in the development of both of these formulations.^{8–10,26} Our approach assumed that individual differences in sensitivity to MPH exist, which may account for differences across patients in the clinically titrated doses (ie, the low, medium, and high doses), but that for any of these titrated doses, the onset of efficacy would be related directly to plasma concentration attributed to the IR component and that the maximum PD response would coincide with the time of the maximum PK MPH level (ie, T_{max}). Based on this PK/PD model, we predicted that, at any time after dosing, the magnitude of response would be related directly to the predicted plasma concentration of MPH at that time such that differences in response for the 2 active formulations (ie, MCD and CON) would be proportional to differences in predicted plasma concentrations. Most of the predictions of the PK/PD model were confirmed: At near-equal daily doses, the larger initial IR MPH bolus of MCD in the morning and the greater proportion of MPH released from the ER component of that formulation during this time were predicted to produce higher expected plasma concentrations compared with CON, and this was reflected in superior outcome during this early postdosing period (1.5–4.5 hours postdose). In the afternoon (6.0–7.5 hours postdose), when the combination of IR and ER components of MCD and CON were predicted to produce approximately the same plasma concentrations of MPH, the 2 treatments did not differ greatly in outcome. Finally, in the early evening (12 hours postdose) when the ER component of CON was predicted to deliver more MPH than that of MCD, CON showed statistical superiority over MCD.

The prediction that stratification by clinical dose would equate the effects of different doses was partially supported by this study. The dose effect was significant for the attention ratings but not for department ratings or PERMP, and the dose \times treatment interactions were not significant at the adjusted significance level of $P < .016$. However, the high correlation of bolus dose with ES in the early morning (1.5 and 3.0 hours) suggests that the patients in the low-dose subgroup might have benefited from higher doses. In addition, the high correlations of effects with the IR MPH dose in the morning sessions are consistent with the expectation of a similar dose-response relationship for the IR components of MPH of either formulation (ie, when adjusted for dose and expected serum concentration, the response to MPH from these 2 formulations does not differ). We believe that this provides a PK/PD explanation for the statistically and clinically significant superiority of MCD versus CON seen at the 1.5- and 3.0-hour time points evaluated in this study.

The a priori hypothesis that provided the rationale for this study was confirmed: When near-equal daily doses are compared for MCD and CON, the average effects of MCD were greater than for CON for the SKAMP department measure across the sessions corresponding to a typical school day (1.5–7.5 hours postdose). Based on the expected relationship of plasma concentration with classroom behavior, this

TABLE 5. AEs Occurring in $\geq 2\%$ of Patients: ITT Population

	Treatment Group		
	MCD (N = 174)	CON (N = 181)	PLA (N = 183)
Gastrointestinal disorders	8 (4.6%)	11 (6.1%)	13 (7.1%)
Abdominal pain upper	6 (3.4%)	8 (4.4%)	6 (3.3%)
Vomiting NOS	1 (0.6%)	1 (0.6%)	4 (2.2%)
Infections and infestations	1 (0.6%)	5 (2.8%)	2 (1.1%)
Injury, poisoning, and procedural complications	6 (3.4%)	3 (1.7%)	5 (2.7%)
Metabolism and nutrition disorders	8 (4.6%)	11 (6.1%)	4 (2.2%)
Anorexia	5 (2.9%)	5 (2.8%)	2 (1.1%)
Appetite decreased NOS	3 (1.7%)	6 (3.3%)	1 (0.5%)
Nervous system disorders	6 (3.4%)	10 (5.5%)	10 (5.5%)
Headache NOS	3 (1.7%)	7 (3.9%)	6 (3.3%)
Psychiatric disorders	12 (6.9%)	13 (7.2%)	17 (9.3%)
Insomnia	3 (1.7%)	3 (1.7%)	6 (3.3%)
Irritability	3 (1.7%)	2 (1.1%)	5 (2.7%)

NOS indicates not otherwise specified. Percents are based on the total number (N) of patients treated in each category. AEs are assigned based on the treatment being received at the start of the AE. Patients are counted only once at body-system level per treatment. Patients with multiple occurrences of the same event are counted once per treatment.

effect can be attributed mainly to both the larger initial IR MPH dose delivered by MCD and, to a lesser extent, to the different release characteristics of the ER MPH portion of each formulation.

In addition, the posthoc analysis of the data by time point indicated a statistically greater effect of CON than either MCD or PLA 12 hours postdose. These differences in school-day efficacy versus early-evening efficacy are noteworthy, and they may help guide clinical practice in the tailoring of treatments for individuals.

The doses of MCD and CON compared in this study meet the published FDA criteria for single-dose bioequivalence of a modified release oral dosage form; however, the results of this study suggest that the PD effects of these 2 formulations are not equivalent. Despite the similarity in overall and maximum exposure to MPH, the differences in early and late exposure to MPH with these 2 once-daily formulations result in detectable and potentially important differences in clinical efficacy during the day. This suggests that single-dose bioequivalence comparisons that are based only on AUC and C_{max} may be insensitive to clinically important differences in PD effects for this class of agents in this patient population.

The site differences in this study deserve some comment, because this is a common finding in multisite studies. The site difference was most prominent for the subjective outcome measures on the SKAMP rating scale, which depend on the training of the observers (which is difficult to equate across sites) and the context of the classroom (which is controlled but still may vary across sites due to class size, physical space, and other factors that may not be standardized). Thus, although the effects of site did not invalidate the overall analyses, the objective secondary measure from the 10-minute math test (PERMP) may provide the most robust surrogate measures of outcome in this multisite study.

The significance of treatment in the analyses of effects at time 0 (immediately after dosing) was due to the superiority of the PLA condition over both

active conditions (MCD or CON). This finding was not predicted by the PK/PD model, and it deserves some comment. A superiority of PLA at time 0 has been noted in almost all the laboratory school studies, but in each case the sample size was too small to result in this interesting but small ES reaching statistical significance. However, with the large sample size used here for the nonequivalence design, the difference in favor of PLA was statistically significant for some measures. We offer 2 speculations about possible mechanisms that could account for this unpredicted difference. First, during the time shortly after dosing, the plasma and brain concentrations of MPH may be very low, and these levels may have a preferential effect on presynaptic compared with postsynaptic dopamine receptors. This may have resulted in the inhibition of dopamine release and a decrease in synaptic dopamine instead of an increase, as was expected when the plasma concentration of MPH reached maximum levels between 1.5 and 3.0 hours after dosing. Second, adaptation effects that produced acute tolerance (tachyphylaxis)²⁷ may linger and still have effects the next day before the next dose of MPH is administered. This may result in a PD “rebound” such that behavior and performance are worse in the morning before the single daily dose is administered.

Limitations

The data for these analyses were from surrogate measures obtained in the laboratory school setting. The laboratory school setting controls for context and timing of the assessments but lacks many features of the natural environment of the home and the school. Thus, it is not certain that the same patterns reported here would be observed in school settings in which an ADHD student would be in a classroom with a majority of the students not affected by this disorder. This is a limitation of the study.

The study was designed to contrast total absorbed daily doses that were approximately equal, although this resulted in differences in the initial bolus doses of the 2 active treatments (MCD and CON). In this

study, doses were not evaluated that were equated for the initial bolus doses of IR MPH, which would provide another test of the PK/PD model. This is another limitation of this study.

The study standardized the treatments and evaluated them in a crossover design. However, in clinical practice, individual differences in efficacy and tolerability direct the clinician to tailor treatment by adjusting dose or supplementing the ER formulations with additional IR doses in the morning or afternoon. These options were not allowed during this study but may be necessary to optimize the effects of MPH on groups of children with ADHD. Thus, the effects of both MCD and CON in the low-dose subgroup were smaller than in the high-dose subgroup, but we do not know whether a higher dose in the low-dose subgroup would have increased the ES. The lack of tailoring to achieve rigorous experimental control may be another limitation of this study.

In this study, plans were made to collect plasma samples from a subset of subjects at 3 sites to allow assay of MPH. Due to practical difficulties at the designated sites, complete samples were not obtained from a sufficient number of subjects to reliably estimate the PK profiles for these patients. Wigal et al⁹ showed that despite lower absolute plasma concentrations of MPH (as expected due to differences in size), the MPH plasma concentration versus time profiles after administration of MCD to children with ADHD were similar to those obtained in healthy adult subjects. In addition, studies with other MPH products indicate that the PK profiles of MPH in adults and school-aged children are qualitatively similar and that there are no apparent age-related differences in absorption, distribution, metabolism, or excretion of MPH.^{28–30} Thus, although the differences found in the PK profiles of MCD and CON by Gonzalez et al¹⁵ are expected to apply to children in this study, the inability to fully confirm this prediction with empirical data are a limitation of this study.

The double-dummy blinding in this study required overencapsulation of CON in a gelatin capsule. As a result, the CON treatment was administered in a form that is not identical to the commercially available product. Thus, the method of blinding we chose for CON, in theory, could have affected the release of the MPH active ingredient. When designing the study, we were aware that overencapsulation of CON in a gelatin capsule had been used successfully to blind a pivotal dose titration study of CON.³¹ Although this indicates that this method of blinding is generally acceptable for this OROS formulation, we took the additional precaution of completing in vitro dissolution testing of our test materials before dosing, and we were able to confirm the absence of a significant effect of gelatin overencapsulation on the release of MPH from CON tablets in vitro.

CONCLUSIONS

The findings from this study suggest that differences in the PK profiles of different MPH products translate into measurable changes in PD profiles, as predicted by the PK/PD model. This finding is im-

portant because it suggests that, under the right conditions (a carefully controlled laboratory school setting), relatively small differences in the pattern of release of the total dose and the corresponding differences in plasma concentrations of MPH produce differences in the behavioral effects of MPH that can be detected and quantified. We believe that these laboratory school findings increase our understanding of the basic properties of these 2 ER MPH formulations, including their similarities and differences, and that this can help to guide the selection of the most appropriate once-daily stimulant treatment for the child with ADHD.

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A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children With Attention-Deficit/Hyperactivity Disorder in the Laboratory School (The Comacs Study)

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A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children With Attention-Deficit/Hyperactivity Disorder in the Laboratory School (The Comacs Study)

James M. Swanson, Sharon B. Wigal, Tim Wigal, Edmund Sonuga-Barke, Laurence
L. Greenhill, Joseph Biederman, Scott Kollins, Annamarie Stehli Nguyen, Heleen H.
DeCory, Sharon J. Hirshe Dirksen and Simon J. Hatch

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