ORIGINAL ARTICLE

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

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Background: The duration of action of the immediate-release formulation of methylphenidate hydrochloride is short (3 to 4 hours), and 3 times daily dosing is thought to maximize effectiveness across a 12-hour day. The initial sustained-release formulations of methylphenidate had reduced efficacy compared with immediate-release methylphenidate and were not well accepted. Tachyphylaxis was hypothesized to account for the reduced effects, and an ascending drug delivery pattern was proposed to overcome this acute tolerance.

Methods: Children with attention-deficit/hyperactivity disorder were evaluated in a laboratory school to characterize onset and duration of the effect of a variety of methylphenidate regimens. In a proof-of-concept study, an experimental ascending profile was established by an initial bolus followed by small increasing doses of immediate-release methylphenidate in capsules administered every 30 minutes for 8 hours. Two proof-of-product studies of a new oral once-a-day formulation to deliver methylphenidate by an osmotic pump process based on OROS (ALZA Corp, Mountain View, Calif) technology (hereafter referred to "OROS-methylphenidate") were conducted: a pharmacokinetic study and a pharmacodynamic study.

Results: The experimental ascending profile matched the effect of the standard regimen of methylphenidate, 3 times daily. In the pharmacokinetic study, OROS-methylphenidate treatment produced a rapid rise followed by increasing plasma concentrations that peaked 7 to 9 hours after administration. In the pharmacodynamic study, OROS-methylphenidate treatment matched the 3 times daily dosing of methylphenidate for onset and duration of efficacy.

Conclusions: These studies demonstrate the translation of a basic science finding (acute tolerance to clinical doses of methylphenidate) into clinical application (the selection of a new drug delivery pattern for methylphenidate). This approach produced a new product (OROS-methylphenidate or Concerta), which proved to have the predicted rapid onset (with 1-2 hours) and long duration of efficacy (10-12 hours) after a single administration in the morning.

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THE STIMULANT medication methylphenidate[1] has been used for almost half a century to treat children with attention-deficit/hyperactivity disorder (ADHD).[2] The efficacy and safety of this clinical practice has been established by decades of clinical use and thousands of research studies.[3] Methylphenidate hydrochloride has been, by far, the most widely used psychotropic medication in child psychiatry.[4]

The immediate-release (IR) formulation of methylphenidate has remained unchanged since its introduction in 1957, despite some shortcomings. For example, IR methylphenidate is relatively short acting,[5,6] and 2 or 3 times a day dosing is recommended to maintain efficacy for 8 to 12 hours.[7-17] The administration of multiple doses of medication each day may be inconvenient and associated with reduced compliance. For children, this usually results in 1 or more doses administered in public at school. In addition to possible embarrassment to the child, the administration of methylphenidate treatment at school creates special problems associated with the storage and handling requirements for a controlled (Schedule II) drug.[12-17]

In the Multimodality Treatment Study of ADHD (MTA),[18] a 3 times daily (TID) regimen of IR methylphenidate was selected as the "state-of-the-art" pharmacological treatment for ADHD. Long-term effectiveness of this treatment regimen was documented over the course of 14 months of treatment in this large randomized clinical trial.[10,19] Secondary analysis[20] documented that the MTA regimen of methyl-

An Example Schedule for the University of California, Irvine, Laboratory School Protocol

Groups 1/2, Time of Day	TID-Methylphenidate Hydrochloride	Experimental	Activity	Classroom/ Mathematics Test
7/7:30 AM			Arrival	
7:30/8 AM	Dose 1	Dose 1		
8/8:30 AM			Cycle 1	Test 1
8:30/9 AM			Blood sample	Class 1
9/9:30 AM	(Peak)	Dose 2	Cycle 2	Test 2
9:30/10 AM		Dose 3	Recess/snack	Recess 1
10/10:30 AM		Dose 4	Cycle 3	Test 3
10:30/11 AM		Dose 5		Class 2
11/11:30 AM	(Trough)	Dose 6	Cycle 4	Test 4
11:30 AM/12 PM	Dose 2	Dose 7	Recess/lunch	Recess 2
12/12:30 PM		Dose 8	Cycle 5	Test 5
12:30/1 PM		Dose 9		Class 3
1/1:30 PM	(Peak)	Dose 10	Cycle 6	Test 6
1:30/2 PM		Dose 11	Recess	Recess 3
2/2:30 PM		Dose 12	Cycle 7	Test 7
2:30/3 PM		Dose 13		Class 4
3/3:30 PM	(Trough)	Dose 14	Cycle 8	Test 8
3:30/4 PM	Dose 3	Dose 15	Recess/snack	Recess 4
4/4:30 PM			Cycle 9	Test 9
4:30/5 PM				Class 5
5/5:30 PM	(Peak)		Cycle 10	Test 10
5:30/6 PM				Recess 5
6/6:30 PM			Pick-up/depart	

Abbreviation: TID, 3 times daily.

phenidate differed from the regimen prescribed by community practitioners, for frequency of dosing (2.9 doses/d vs 2.1 doses/d) and total daily dose (32.8 mg/d vs 18.7 mg/d).

Despite the impressive efficacy of IR methylphenidate treatment documented by the MTA,[10,19,20] problems remain that are inherent to the multiple doses per day. An early attempt was made to overcome these shortcomings with a sustained-release (SR) formulation of methylphenidate based on a wax-matrix delivery system. This SR methylphenidate formulation[12] was approved for the treatment of ADHD over a decade ago, but it had delayed onset of action and reduced efficacy compared with the IR methylphenidate formulation and was not well accepted in clinical practice.[16,17]

In 1993, a research program, supported by ALZA Corp, Mountain View, Calif, was initiated at the University of California, Irvine (UCI) to address these problems. The initial step was to conduct "concept discovery" study to understand some basic properties of the time course of responses to IR methylphenidate treatment. The results of this study[11] showed that a constant (zero-order) drug delivery pattern did not maintain efficacy across the day; tachyphylaxis (acute tolerance) was proposed to account for this observation. This concept implied that the reduced efficacy of existing SR methylphenidate formulations might be the result of nonascending (ie, flat or descending) drug delivery profiles, and that an ascending (first-order) drug delivery profile would overcome the hypothesized acute tolerance. The research program required methodological innovations[21-23] (eg, development of the UCI Laboratory School Protocol and the application of pharmacokinetic-pharmacodynamic [PK/PD] modeling), which will be reviewed to provide background for the proof-of-concept and proof-of-product studies that will be reported herein.

THE UCI LABORATORY SCHOOL PROTOCOL

The UCI Laboratory School Protocol provides tight control of timing and context of observations so that subjective and objective measures of methylphenidate efficacy can be made precisely and repeatedly across the day.[21] In this protocol, children already diagnosed as having ADHD and who have a clinical history of beneficial response to stimulant medication are evaluated. The clinical diagnosis is confirmed by a structured psychiatric interview (eg, the Diagnosis Interview Schedule for Children). The established treatment is used as an active control condition in a crossover design that also includes an inactive (placebo) control and experimental conditions. Typically, each condition is established for 1 week, starting on Sunday. Once a week (usually on Saturday) groups of children with ADHD attend the laboratory school, where they are evaluated for up to 12 hours (eg, 7 AM to 7 PM). Each test day consists of cycles of precisely timed activities designed to be repeated (**Table**). In studies reported herein, a 1-hour cycle of activities was used, consisting of capsule administration (1 minute), computer mathematics tests or library quiet time (9 minutes), individual classroom seatwork (20 minutes), capsule administration (1 minute), library quiet time or computer mathematics test (9 minutes), and group classroom activity (20 minutes).

The Swanson, Kotkin, Agler, Mylnn, and Pelham (SKAMP)[22] teacher-rating scale was developed to evaluate behavior over a short period (eg, a classroom period).[21] The SKAMP items describe specific behaviors that are expected in the classroom related to attention (eg, getting

started, sticking with activities, completing work, and stopping for transition) and deportment (ie, remaining quiet, remaining seated, interacting with other students, and interacting with the teacher) rather than the general behaviors described by most other rating scales used to assess children with ADHD. Each item is rated on a 7-point impairment scale,[20] and an average rating per item is calculated for the subscales of Attention and Deportment. Test-retest reliability and sensitivity to treatment with stimulant medications have been demonstrated for the SKAMP subscales.[22,23] To supplement these subjective classroom ratings, short 10-minute objective tests (eg, a memory scanning test[11] or a mathematics test[21]) were designed to be administered by computer after or on paper during each classroom probe, and speed and accuracy of response on these tasks were used as measures of academic productivity. By repeating the subjective and objective measurements at regular times across each test day, the time course of effects of methylphenidate treatment (relative to placebo) can be estimated.

The first concept discovery study used the UCI Laboratory School to conduct a "sipping" study,[11] in which methylphenidate or placebo was administered in capsules at 30-minute intervals for 8 hours (Table). We used PK/PD modeling to define the dosing regimens that would generate flat and ascending PK profiles, which we contrasted with a standard clinical regimen of administration of IR methylphenidate twice daily (BID). We addressed 2 basic questions related to key patterns of delivery of methylphenidate treatment: "Is a bolus delivery of methylphenidate necessary to elicit the full clinical efficacy?" and "Will a constant rate of delivery of methylphenidate treatment maintain full efficacy over time?"

Multiple PD measures of efficacy (ie, teacher ratings for each classroom session and academic productivity tests after each classroom session) at multiple times across the day documented[11] large effect size estimates (>1) at the peak and trough time points for the BID condition, and this provided a "ruler" to gauge the magnitude of effects from the other 2 experimental conditions (ie, ascending and flat). The low initial serum concentration of the ascending condition produced smaller effect sizes in the morning (as expected), but the gradually increasing serum concentrations of the ascending condition produced effect sizes in the afternoon that matched the effect size estimates for the BID condition, indicating that a bolus dose was unnecessary for full efficacy. The constant serum concentration of the flat condition resulted in the loss in the afternoon of about 40% of the average effect size observed in the BID condition, indicating that a zero-order drug delivery pattern did not maintain full efficacy and suggesting acute tolerance to methylphenidate treatment.[24]

PK/PD MODELING

In a 3-compartment PK/PD model, we made provisions for a lag due to gastrointestinal absorption time and the time for blood flow to distribute methylphenidate in plasma to the site of action in the brain.[25,26] We estimated the theoretical methylphenidate concentration at the effect site (Ce), which was assumed to produce a cascade of processes that result in the indirect agonist effect at the neural level (eg, blockade of the dopamine transporter and increase in dopamine at the synapse). This is considered the basis for the observed effects at the behavioral level (eg, decrease in ADHD symptoms). We also assumed that acute tolerance would start to develop when methylphenidate reached the brain, and we designated a second theoretical concentration at an antagonist site (Cant) to account for the observed loss of efficacy over the day.

This PK/PD model was used to predict profiles for 3 plausible drug delivery patterns under consideration for delivery of methylphenidate by the OROS osmotic technology (hereafter referred to as "OROS-methylphenidate") (**Figure 1**): a bolus pattern based on a TID regimen (10 mg at 7:30 and 11:30 AM and 3:30 PM) that would extend the duration of efficacy compared with the BID regimen; a flat pattern based on the prototype drug delivery profile for SR methylphenidate hydrochloride formulations (8 mg at 7:30 AM, followed by small constant 1.25 mg doses at 30-minute intervals); and an ascending pattern based on the concept of acute tolerance (8 mg at 7:30 AM, followed by small and increasing doses of 1.3 to 2.6 mg at 30-minute intervals). For the flat condition, the emergence of acute tolerance was predicted to gradually reduce the constant agonist effect, producing the declining profile of the net effect ($Ce_f - Cant_f$). For the ascending condition, the rate of increase in drug delivery was set to produce an ascending agonist effect to overcome the emerging antagonist effect, so the net effect ($Ce_a - Cant_a$) was predicted to remain constant over the day.

Before embarking on an expensive technology development program to modify the existing OROS technology to achieve the ascending drug delivery pattern, a proof-of-concept study was conducted to provide an empirical test of theoretical prediction that this PK profile would produce constant behavioral effects across the day. For the proof-of-product studies, the round OROS that provides a zero-order (flat) delivery profile was modified to be a capsule with an overcoat of IR methylphenidate and a drug reservoir consisting of a bilayer of methylphenidate and a separate osmotic polymer, surrounded by a semipermeable membrane. When taken orally as the single administration in the morning, the overcoat of OROS-methylphenidate was designed to deliver an initial bolus of IR methylphenidate to produce a rapid rise in serum concentrations of methylphenidate. When in contact with water in the gastrointestinal tract, the shape, the properties of the membrane, the osmotic polymer, and the drug reservoir were designed to create an osmotic pump to deliver methylphenidate at a first-order rate (ie, an ascending profile) for about 10 hours after administration. For the proof-of-product studies, 18-mg tablets of OROS-methylphenidate were manufactured, using a 4-mg overcoat and 14 mg in the drug reservoir. Multiple tablets were administered to achieve the higher (36- and 54-mg) doses.

METHODS

Children aged 7 to 13 years, who met *DSM-IV* criteria for a diagnosis of ADHD and who were being treated with 5 to 15 mg of IR methylphenidate hydrochloride administered BID or TID, were recruited and evaluated in protocols approved by the UCI investigational review board. Double-blind procedures were implemented by administration of methylphenidate or placebo

in capsules. Subjective ratings of Attention and Deportment from the SKAMP rating scale and the objective performance scores on the mathematics test (Speed and Accuracy) were used as surrogate measures of efficacy. These measures were evaluated in an analysis of variance (ANOVA) model with within-subject (repeated measure) factors in a crossover design.

Cohorts of children with ADHD were evaluated over multiple, nonconsecutive test days in the UCI Laboratory School.[21] On the first day, the children were introduced to the staff and to each other, divided into 2 classes of 8 students based on age, and familiarized with the facility and the laboratory school. On each of the test days, children had breakfast at home and arrived at the Child Development Center school around 7 AM. A 1-hour cycle of activities was repeated across the test day (Table). Classroom behavior was evaluated during classroom probes, and after each of these sessions, teachers completed the classroom SKAMP rating scale. The subjective ratings of Attention and Deportment were specified as the primary outcome measures for onset and duration of efficacy. The computerized mathematics test was administered during key cycles, and objective Speed and Accuracy scores were specified as secondary outcome measures to complement the subjective ratings of behavior in the classroom.

PART 1: PROOF OF CONCEPT

Two cohorts of 16 children were recruited for this study. Methylphenidate or placebo was given in capsules at 30-minute intervals throughout the day, with the methylphenidate content of the capsules set to establish 2 drug conditions: standard (TID) and experimental (ascending) regimens. In the TID regimen, 3 of the capsules (those administered at 7:30 and 11:30 AM and 3:30 PM) contained equal doses of IR methylphenidate. The per-administration dose was selected based on each subject's clinically titrated morning dose rounded off to the nearest 5-mg dose (ie, 5, 10, or 15 mg), which resulted in a total daily dose of 15, 30, or 45 mg. In the ascending regimen the first capsule (administered at 7:30 AM) contained 80% of each child's morning dose (ie, 4, 8, or 12 mg), the second capsule contained placebo, and subsequent capsules contained small but increasing doses of methylphenidate prescribed by PK/PD modeling to counteract acute tolerance. This accumulated to total daily doses of 18, 36, or 54 mg, respectively. The PK/PD model predicted the profiles for the 3 theoretical concentrations (Ce, Cant, and Ce – Cant) that are shown in Figure 1 for the TID and ascending dosing regimen. The time course of efficacy documented by surrogate measures in the UCI Laboratory School were expected to follow the time course of the net effects (Ce – Cant) in the PK/PD model.

In the ANOVA, a 3 × 5-factorial design was used with fixed-effect factors of treatment (TID, ascending, and placebo) and session (5 structured classroom sessions scheduled to coincide with the TID peaks and troughs expected to occur at 9 and 11 AM and 1, 3, and 5 PM). Random effect factors for sequence (orders 1-6) and period (test days 1, 2, and 3) were included to account for intersubject and intrasubject variations.

PART 2: PROOF OF PRODUCT

For the PK study, a cohort of 16 subjects was evaluated in a 3-way crossover study of equivalent doses of OROS-methylphenidate and TID-methylphenidate administered in the fasting state and the OROS-methylphenidate dose administered with a high-fat breakfast. In the UCI Laboratory School protocol, a 1-hour cycle of activities was repeated 10 times (Table). Each cycle included provisions for a blood sample, a classroom session, or a recess period. Each subject's established clinical dose was used to determine whether a subject received a low (5-mg TID = 15 mg/d), medium (10-mg TID = 30 mg/d), or high (15-mg TID = 45 mg/d) dosage of IR methylphenidate hydrochloride, and a conversion algorithm was used to set the corresponding OROS-methylphenidate dosage (18, 36, or 54 mg/d).

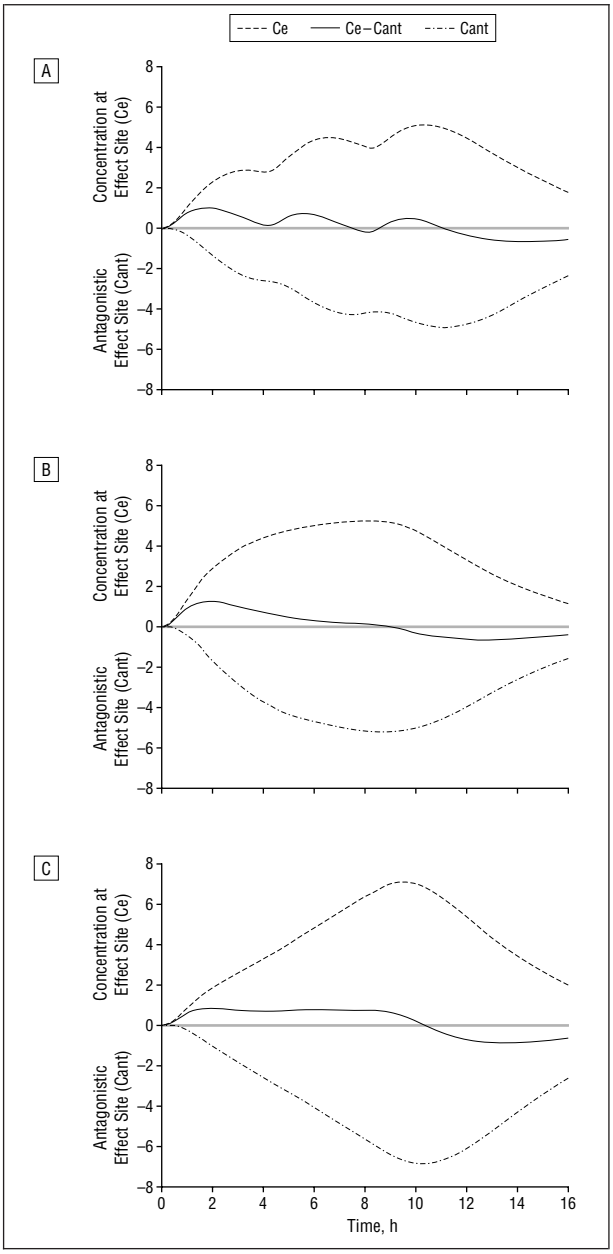

Figure 1. Effect site (Ce), antagonist site (Cant), and net (Ce – Cant) profiles from pharmacokinetic-pharmacodynamic modeling for the following 3 conditions: A, those receiving a regimen of immediate-release methylphenidate hydrochloride 3 times daily; B, those receiving a bolus that created a flat pattern based on the prototype drug delivery profile for sustained-release methylphenidate hydrochloride formulations (ie, 8 mg at 7:30 AM, followed by small constant 1.25-mg doses at 30-minute intervals); and C, those receiving a bolus that created an ascending pattern based on the concept of acute tolerance (8 mg at 7:30 AM, followed by small and increasing doses from 1.3 to 2.6 mg at 30-minute intervals). See the "PK/PD Modeling" subsection of the introductory section for an explanation of the flat and ascending net effects.

For the PD study, 2 cohorts of 32 subjects were recruited for randomized, 3-way, crossover trial in which a double-blind, double-dummy procedure was used to disguise the 3 treatments (OROS-methylphenidate, TID-methylphenidate, and placebo). The treatments were established by contents of 2 capsules administered at 7:30 AM and single capsules at 11:30 AM and 3:30 PM. The low, medium, or high methylphenidate dose

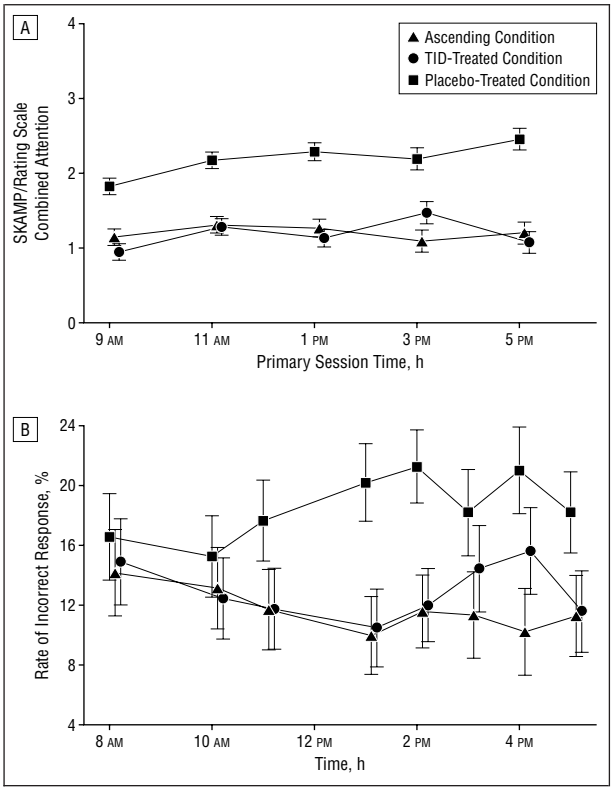

Figure 2. Results of the proof-of-concept study: the Attention and Performance subscales of the Swanson, Kotkin, Agler, Mylnn, and Pelham (SKAMP)[22] rating scale and the percentage of errors made on the computerized mathematics test.

regimens were set based on each individual's clinical history. Each treatment began on a Sunday and ended 1 week later.

In the natural environment, effectiveness was measured with the Conners, Loney, and Milich (CLAM) rating scale,[20,21,27] which was completed by a parent and a teacher each Friday to summarize the child's behavior at home and at school during the previous week. The 16-item CLAM rating scale includes the 5 Inattention/Overactivity (I/O) items and 5 Oppositional/Defiance (O/D) items of the IOWA (Inattention and Overactivity With Aggression) Conners rating scale. Each item was rated on a 4-point scale (1, not at all; 2, just a little; 3, pretty much; and 4, very much) and summary scores (sum of the I/O items and sum of the O/D items) were calculated for the 2 subscales. The I/O rating by the community schoolteacher was specified a priori as the primary outcome measure of this study. The Swanson, Nolan, and Pelham (SNAP) rating scale[19] was completed by the community schoolteacher and the parent at the end of each week. In addition to the effectiveness and efficacy measures, adverse effects were actively solicited and assessed and information about sleep, appetite, and tics was collected using a parent questionnaire.

On each Saturday, the cohort attended the UCI Laboratory School and followed the schedule shown in the Table. The laboratory schoolteacher completed the SKAMP rating scale after the multiple classroom sessions of each laboratory school day. Vital signs (blood pressure and pulse rate) were obtained after each classroom session.

A mixed-effects ANOVA model was used for the analysis of the efficacy measurements. This ANOVA model included the fixed-effect factors of treatment, sequence, and period, and random-effect interpatient and intrapatient factors. Paired comparisons were also performed between placebo and each of the active drug conditions, and between the 2 active drug conditions. Effect sizes were calculated for each treatment for each efficacy measure as the difference between the least squares mean of each active treatment and placebo divided by the estimate of intrapatient variation (root-mean-square error of the ANOVA mixed-effects model).[28,29]

RESULTS

PART 1: PROOF OF CONCEPT

Twenty-eight boys and 4 girls (aged, 7-12 years; mean age, 9.9 years) were enrolled in this study. At baseline, this group was taking an average initial methylphenidate hydrochloride dose of 11.6 mg (0.4 mg/kg), and the average absolute daily dose was 28.9 mg (0.9 mg/kg per day). Based on prestudy initial (morning) dose, each subject was assigned to a low 5-mg dose (n=7), an intermediate 10-mg dose (n=17), or a high 15-mg dose (n=8) condition. Two children left the study prematurely because of other personal commitments, so 30 of the 32 children enrolled in this trial completed all 3 treatments and were included in the analysis.

The results are shown in **Figure 2**A, where the average SKAMP attention ratings for each of the treatments are presented for the 5 classroom sessions timed to coincide with the expected peaks and troughs of the TID condition. In the ANOVA, the main effect of treatment was significant ($F_{2,424}=125$; $P<.001$). Paired comparisons revealed that teacher ratings of attention in both the TID and ascending conditions differed from placebo at each of the 5 time points. An effect size (difference from the placebo divided by a pooled estimate of the SD from the ANOVA) was calculated for each classroom session. The overall (average) effect sizes were large (>1.5) for the TID and ascending conditions, which did not differ significantly in the specific comparisons of onset of efficacy (at the 9 AM session, 1½ hours after the morning TID dose) and duration of efficacy (at the 5 PM session, 3½ hours after the last TID dose).

The average scores for accuracy of performance on the objective mathematics test are shown in Figure 2B. The youngest children could not solve the 2-digit mathematics problems as they were presented on the computer, so only 23 of the 31 subjects contributed data on this task. The main effect of condition was significant in the ANOVA of speed ($F_{2,518}=49.2$, $P<.001$) and accuracy ($F_{2,518}=42.9$; $P<.001$). Paired comparisons revealed that performance was superior in the TID and ascending conditions compared with performance in the placebo condition. Individual comparisons at each time point confirmed that the mathematics performance in the TID and ascending conditions was superior compared with the placebo condition after the 10 AM test and did not differ significantly from each other at any of the test times. In comparison to placebo, the overall effect sizes were 0.9 for speed and 0.7 for accuracy in the TID condition and 0.9 for both speed and accuracy in the ascending condition, which confirms the general pattern reflected by the subjective teacher ratings.

The effects of treatment on blood pressure and heart rate were evaluated by the ANOVA. Both the TID-methylphenidate and experimental conditions produced small but statistically significant ($P<.05$) increases simi-

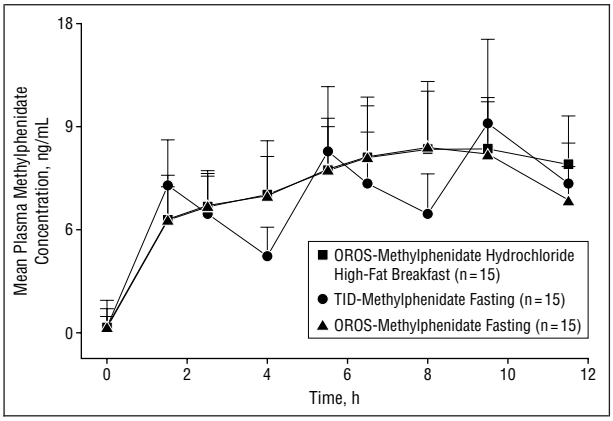

Figure 3. The pharmacokinetic profiles from a 3-way crossover study of immediate release OROS–methylphenidate hydrochloride administered with a (high-fat breakfast) and without (fasting) food, and TID (3 times daily)–methylphenidate administered in the fasting state. OROS is a new oral once-a-day formulation to deliver methylphenidate by osmotic pump process based on OROS technology (ALZA Corp, Mountain View, Calif).

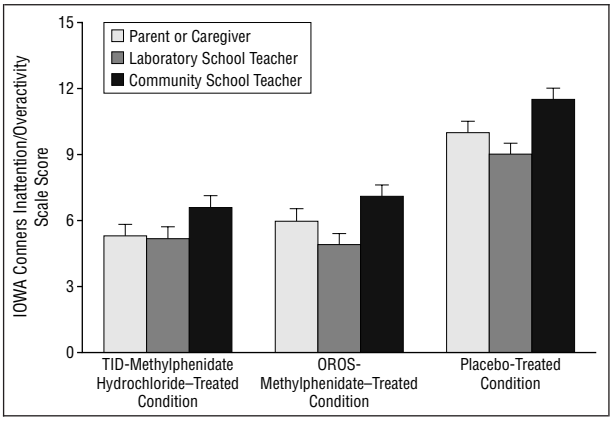

Figure 4. IOWA (Inattention and Overactivity With Aggression) Conners rating scale from 3 sources (parent, University of California, Irvine, Laboratory School teacher, and community schoolteacher) in the proof-of-product study of the OROS-methylphenidate hydrochloride–treated condition, TID (3 times daily)–methylphenidate–treated condition, and placebo-treated condition.

lar to those seen with IR methylphenidate.[16] Statistically significant drug effects on systolic blood pressure (3-4 mm Hg), diastolic blood pressure (3-5 mm Hg), and heart rate (4-7/min) were observed at 9:30 AM and 1:30 and 4:30 PM.

On the adverse effects rating scale, teachers indicated that some adverse effects (eg, irritability, motor tics, and buccolingual movements) decreased in the medication conditions relative to the placebo condition. These decreased ratings may seem incongruous with the label and concept of "adverse effect," but this pattern is consistent with a double-blind titration trial of methylphenidate effects in a large sample of more than 200 children in the MTA.[20] The teachers noted appetite loss in more subjects in the medication conditions (TID, n=6; ascending, n=7) than in the placebo condition (n=1); this was also consistent with the findings of the MTA titration trial. The frequencies of parent reports of somatic complaints (primarily headaches or stomachaches) were similar in the TID methylphenidate (n=9), ascending (n=5), and placebo (n=8) conditions.

Parents described only 60% of children as having their usual evening food intake in both medication conditions, but this did not differ from placebo (59%). Parent ratings indicated good or excellent sleep quality for 90% of children in the placebo condition, which did not differ from the TID and ascending conditions (both 87%). Sleep onset (as determined by an actigraph [MiniMotion Logger; Ambulatory Monitoring, Ardsley, NY], a motion detector worn on the wrist for the week of each condition) was delayed slightly in the medication conditions (ascending, 0.65 h; TID, 0.55 h) compared with the placebo condition (0.11 h), and these differences were statistically significant. A detailed accounting of the sleep assessment will be presented in a separate paper.

PART 2: PK AND PD PROPERTIES OF OROS-METHYLPHENIDATE TREATMENT

In the PK study, methylphenidate concentration data were obtained for 15 of the 16 children with ADHD. The PK results are shown in **Figure 3**. The expected concentration profile for TID-methylphenidate was obtained, with a peak about 2 hours after each bolus dose and a rapid decline to about half the peak concentration before the next dose (as predicted by a PK half-life of about 2 to 3 hours). Compared with the TID-methylphenidate, the concentration profile for OROS-methylphenidate showed a slightly lower initial peak about 2 hours after the initial capsule (as expected by the 80% formula used to set the dose of the overcoat), but gradually rising concentrations after the initial peak produced a concentration that almost equaled the third peak of the TID-methylphenidate condition at the end of the day. There was no significant difference between the 2 food conditions of OROS-methylphenidate (fasting and high-fat breakfast) at any time point evaluated in this study. This verified that a single morning dose of OROS-methylphenidate achieved the targeted ascending plasma concentration profile set by PK/PD modeling, without the food effect.

The PD study enrolled a sample of 64 children having a *DSM-IV* diagnosis of ADHD (82.8% combined type) who were between 6 and 12 years of age (mean [SD] age, 9.2 [1.8] years) and were preponderantly male (81.3%) and white (82.8%). One patient never entered the treatment phase of the study and 2 patients discontinued treatment early (1 for a protocol violation and 1 because the parents withdrew consent).

The ANOVA of the primary outcome measure (the community school teacher's IOWA Conners I/O rating) showed a significant treatment effect (type III $F=54.42$; $P<.001$). The least significant difference paired comparisons revealed that ratings were lower for both OROS-methylphenidate (effect size, 1.69; $P<.001$) and TID-methylphenidate (effect size,1.57; $P<.001$) treatments than for placebo (I/O ratings, 6.54, 6.89, and 11.60, respectively, with a pooled SD of 3.0). The 2 active treatments did not differ significantly ($P=.32$) from each other. The effect sizes for the 2 other sources (parent and laboratory schoolteacher) showed similar magnitudes of effect (**Figure 4**). For the parent ratings, the I/O effect sizes (significant at $P<.001$) were 1.53 for OROS-methylphenidate and 1.31 for TID-methylphenidate treatments compared with placebo (I/O ratings, 5.32, 5.97, and 9.90,

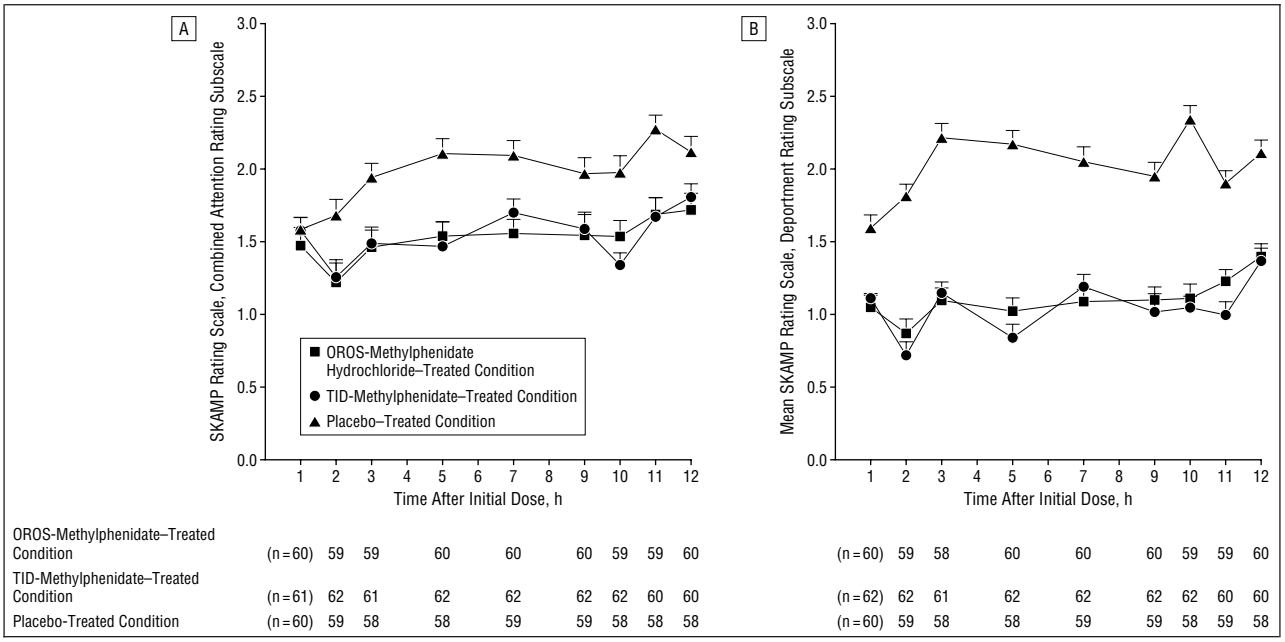

Figure 5. Attention ratings using the Swanson, Kotkin, Agler, MyInn, and Pelham (SKAMP)[22] rating scale by the University of California, Irvine, Laboratory School showing the onset and duration of OROS-methylphenidate hydrochloride–treated condition and TID (3 times daily)–methylphenidate–treated condition in the proof-of-product study. OROS is a new oral once-a-day formulation to deliver methylphenidate by osmotic pump process based on OROS technology (ALZA Corp, Mountain View, Calif).

respectively, with a pooled SD of 3.0). For the laboratory schoolteacher, the I/O effect sizes were 1.35 for OROS-methylphenidate and 1.52 for TID-methylphenidate treatments compared with placebo (I/O ratings, 5.25, 4.82, and 8.77, respectively, with a pooled SD of 2.6).

Figure 5 presents the PD efficacy data from the laboratory classroom. Onset of effect was similar for OROS-methylphenidate and TID-methylphenidate treatments. For the SKAMP measure of Attention, significant effects emerged by 2 hours after initial dosing in both medication conditions, and using the pooled SD estimate from the ANOVA, the magnitude of the drug effects was similar: OROS-methylphenidate (effect size=0.84) and TID-methylphenidate (effect size=0.77) treatments compared with placebo (Attention ratings, 1.23, 1.26, and 1.68, respectively, with a pooled SD of 0.54). For the SKAMP measure of Deportment, significant effects emerged earlier (by 1 hour after initial dosing) for both medication conditions, and the magnitude of these drug effects was also similar for OROS-methylphenidate (effect size=1.10) and for TID-methylphenidate and (effect size=1.27) treatments compared with placebo (Deportment ratings, 0.87, 0.72, 1.82, respectively, with a pooled SD of 0.86). Significant effects were maintained over the day and still present 12 hours after the initial dose, for measures of Attention (effect size=0.53) and for TID-methylphenidate and (effect size=0.53) treatments compared with placebo (Attention ratings, 1.72, 1.82, and 2.13, respectively, with a pooled SD of 0.57), as well as for measures of Deportment for OROS-methylphenidate (effect size=0.85) and for TID-methylphenidate (effect size=0.89) treatments compared with placebo (Deportment ratings, 1.40, 1.37, and 2.14, respectively, with a pooled SD of 0.87). The effect sizes at the intermediate assessment points were all significant at $P<.001$, for both medication conditions and both subscales of the SKAMP rating scale.

Adverse effects from treatment were minimal in this study. The most common included headache and stomachache (abdominal pains). OROS-methylphenidate and TID-methylphenidate treatments had similar adverse effect profiles. The ANOVA of vital signs showed slight and similar increases in blood pressure and pulse rate for both OROS-methylphenidate and TID-methylphenidate treatments.

COMMENT

This article presents findings from a series of studies designed to evaluate the PK/PD characteristics of methylphenidate treatment. A laboratory school protocol and surrogate measures of efficacy were developed and used in concept discovery studies, which suggested that acute tolerance occurred after oral administration of methylphenidate. Based on this theoretical notion, we speculated that then-available SR methylphenidate formulations would not achieve a concentration at the effect site fast enough to produce a rapid onset of action, and that once constant concentration was achieved and maintained for any dose, the PD effect would decline owing to acute tolerance. The PK/PD modeling provided the target for a novel drug delivery pattern to overcome these shortcomings: an initial bolus to elicit a rapid response and an ascending pattern of drug delivery to maintain constant effects.

The proof-of-concept study demonstrated the safety and efficacy of this experimental drug delivery profile designed to overcome acute tolerance. OROS-methylphenidate was produced to deliver this theoretically optimal delivery profile in a once-a-day formulation, and a proof-of-product study demonstrated its effectiveness in the natural environment as well as its efficacy in the Laboratory School. This work informed the design of traditional clinical trials, which followed and led to the approval by the Food and

Drug Administration of OROS-methylphenidate (Concerta) for the treatment of ADHD.[30]

The PK/PD modeling in this study was based on simulations of plasma concentration, not actual (measured) drug concentrations. This limitation was accepted in the early phases of the research program to avoid unnecessary collection of blood samples from children who participated in the concept studies. However, if actual PK data were available for the modeling, it is possible that a more precise estimate of the optimal drug delivery profile could have been derived from the concept studies.

The children with ADHD in the proof-of-concept and proof-of-product studies were selected based on a history of clinical response to stimulant medication, and this limits the extrapolation of the findings to the drug-naive population. The response rates and the manifestation of adverse effects must be interpreted in this context.

The surrogate measures obtained repeated across the day in the laboratory school were developed and used to obtain estimates of onset and duration of efficacy in the proof of product studies. A more ecologically valid procedure would be to observe the children with ADHD at multiple time points in the home and school to estimate effectiveness. This limitation was accepted in the proof-of-product study, based on an assumption that the duration of effectiveness based on measures from the natural environment would be similar to the duration of efficacy based on surrogate measures.

The tolerance model that emerged from the concept studies is complex, and the tolerance effect is subtle. Other explanations of the loss of efficacy across the day may provide an equivalent or better account of the findings. Instead of consideration of alternative hypotheses from the concept studies, we selected 1 hypothesis that we tested in proof of concept studies. A comparison of 2 alternatives hypotheses may have yielded a better understanding of the mechanisms of action and the PD properties of methylphenidate.

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