A Pharmacokinetic/Pharmacodynamic Study Comparing a Single Morning Dose of Adderall to Twice-Daily Dosing in Children With ADHD

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ABSTRACT

Objective: To determine the pharmacokinetic and pharmacodynamic properties of once-daily versus twice-daily doses of Adderall®. **Method:** Following a 1-week wash-out, 12 subjects with attention-deficit/hyperactivity disorder (ADHD) entered a double-blind crossover study comparing two conditions: QD (10 mg of Adderall at 7:30 A.M. and placebo at noon) or BID (10 mg of Adderall at 7:30 A.M. and at noon). At two sites, cohorts of six subjects each were assessed on two different days by a 12-hour laboratory school protocol. Plasma concentrations of *d*- and *l*-amphetamine, vital signs, teacher ratings of classroom behavior on the SKAMP, and 10-minute Math Test performance were measured repeatedly over 12 hours. An analysis of variance used center, subject-within-center, condition, and time-after-second-dose as independent variables. **Results:** The pharmacokinetic profiles revealed similar morning concentrations of *d*- and *l*-amphetamine. However, concentrations were twice as high in the afternoon for BID as QD. The two conditions showed similar pharmacodynamic profiles in the morning, although improvement in math performance and behavior was maintained into the afternoon only in the BID condition ($p < .05$). **Conclusions:** This study suggests that twice-daily dosing of Adderall may be an effective strategy for afternoon control of attention and deportment for children with ADHD. *J. Am. Acad. Child Adolesc. Psychiatry,* 2003, 42(10):1234–1241. **Key Words:** attention-deficit/hyperactivity disorder, laboratory school protocol, amphetamine, Adderall, pharmacokinetic, pharmacodynamic.

For more than 50 years, stimulant medication has served as the first-line treatment for attention-deficit/hyperactivity disorder (ADHD), which is estimated to affect 3% to 5% of the school-age population (American Academy of Child and Adolescent Psychiatry, 2002; American Psychiatric Association, 1994; Greenhill, 1998; Hinshaw, 1994; Swanson, 1992). Although amphetamine (AMP) was the first stimulant used (Bradley, 1937), in the 1970s methylphenidate became the primary medication for the treatment of ADHD, and by the mid-1990s approximately 80% of prescriptions for stimulants to treat ADHD were for methylphenidate (Swanson et al., 1995). Since the late 1990s there has been an increase in the use of a racemic formulation of AMP (75% *d*-AMP and 25% *l*-AMP), which was reintroduced and marketed as Adderall®.

Initially, a once-a-day (QD) dosing regimen was recommended for Adderall. To our knowledge, there were no pharmacodynamic (PD) or pharmacokinetic (PK) Adderall data in children previously published to support this claim. PK studies of Dexedrine (*d*-AMP) in ADHD children (Brown et al., 1978, 1979, 1980) have demonstrated a shorter T½ (about 7 hours) than expected from the PK studies of adults.

PD studies of Adderall (Pelham et al., 1999; Swanson et al., 1998a) suggested that higher doses of AMP might have a longer duration of action. A double-blind

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crossover study in a laboratory school protocol (LSP) that compared four doses of Adderall (5, 10, 15, and 20 mg) with an inactive placebo control and an active control (a clinical dose of MPH) (Swanson et al., 1998a) reported that higher doses of Adderall extended the calculated length of action (from 3.5 to 6.4 hours). However, this was at the expense of an increase in the time of peak effect (from 1.5 to 3.0 hours) in the highest-dose condition (20 mg). Even though higher doses extended the half-life more than 50%, the total coverage period was less than 7 hours, hardly long enough for a standard school day.

We speculated that by using a 10-mg immediate-release (IR) BID dosing regimen instead of a 20-mg IR QD dose, it would be possible to extend the length of action in the afternoon without producing a high AMP concentration in the morning, which could produce increased side effects in a 6-year-old child with ADHD due to the linear relationship between side effects and dose for amphetamines. A double-blind trial of QD and BID conditions was run to compare their PK and PD effects in the controlled LSP setting to address this question and to investigate the basic mechanism involved in response to Adderall.

METHOD

The study was conducted at two academic medical centers (University of California at Irvine and Columbia University), whose institutional review boards approved all procedures prior to subject recruitment. All subjects provided written or verbal assent for study participation; parents provided written consent for their child's enrollment.

Subjects

Subjects meeting the following inclusion criteria were recruited: (1) age 7 to 12 years; (2) meet the diagnostic criteria for *DSM-IV* ADHD (combined or hyperactive-impulsive subtype as determined by clinician evaluation and selected modules of the Diagnostic Interview Schedule for Children, Version IV-Lifetime) (Shaffer et al., 1996); (3) have a history of a clinically significant response to typical doses of methylphenidate (5–20 mg, BID or TID); (4) have parental confirmation that the child could attend the two full-day test sessions, 1 week apart, that were scheduled.

Exclusion criteria rejected subjects with (1) blood pressure and pulse outside the 95th percentiles for age and gender; (2) abnormalities on physical examination, including the presence of an acute or chronic disease such as anemia, hypertension, glaucoma, or hyperthyroidism, or a medical history of a nonfebrile seizure disorder; (3) family history of suspected substance use disorders (excluding nicotine); (4) family history of Tourette's disorder; (5) use of clonidine, anticonvulsant medications, or other CNS medications; (6) history of an adverse reaction or nonresponse to Adderall or hypersensitivity to any AMP product; (7) excessive fear of needles; (8) history of aggressive behavior incompatible with regular classroom activities, as shown by a diagnosis of childhood-onset persistent conduct disorder; (9) history of comorbid psychosis, bipolar illness, pervasive developmental disorder, tic disorders, severe obsessive-compulsive disorder, severe depression, conduct disorder, panic disorder, current suicidal ideation, or severe anxiety; (10) Full Scale IQ less than 80 as assessed by the WISC III. Females who had reached menarche were also excluded.

Laboratory Classroom Protocol

The LSP setting was designed to control the timing and context of repeated observations over an entire day of testing (Swanson et al., 1998b; Wigal et al., 1998). For this study, the standard LSP developed at the University of California at Irvine (Swanson et al., 2000) was transferred to a second site (Columbia University).

Each site tested a cohort of six subjects in the LSP on two consecutive Saturdays. Before the two LSP test days, each child was invited to come to the site to become familiar with the LSP procedures. On each LSP test day, subjects arrived at the laboratory school at approximately 7 A.M., and indwelling catheters were placed before capsules were administered at 7:30 A.M. The daily schedule consisted of alternating classroom, recess, and other activities. The classroom sessions began after the morning dose administration (8 A.M.) and occurred every hour for the next 3 hours (9, 10, and 11 A.M.). Classroom sessions were scheduled in the afternoon following the noon dose and began within an average time of 0, 1.5, 3.5, and 6 hours after the second dose (i.e., spread across the afternoon at noon, 1:30, 3:30, and 6:00 P.M.). Each classroom period lasted a total of 30 minutes and was directed by two teachers for a cohort of six subjects. In addition, each classroom contained two observers (trained to be reliable) who rated classroom behavior after each session using a system described previously (Swanson et al., 2000). Outside of the classroom period, a separate staff (counselors) directed and supervised the nonclassroom activities across the day. No behavioral treatments were used during the LSP days.

Medication Dosing

Prior to the two test days, subjects underwent a 6-day washout of stimulants and other psychotropic medications. On each LSP test day, a pharmacist or a physician administered a capsule with an initial 10-mg dose of Adderall to each subject at 7:30 A.M. (30 minutes before breakfast) and a second capsule at noon (30 minutes before lunch), which contained either 10 mg of Adderall (the BID condition) or placebo (the QD condition). The order of the two conditions (BID-QD or QD-BID) was randomized across subjects and was established under double-blind conditions.

PK Sampling

On arrival to the initial and final analog classroom sessions, indwelling catheters for plasma sampling were inserted into an antecubital vein in each subject. Pharmacokinetic sampling was conducted predose and 0.5, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, and 24 hours following dosing. Blood samples were collected in 10-mL EDTA Vacutainer tubes and plasma was prepared immediately by centrifugation of the blood samples. Plasma was transferred and stored at approximately −20°C prior to shipping for analysis.

Analytic Methods

Plasma samples were analyzed for AMP concentrations (*d*-AMP and *l*-AMP) by high-performance liquid chromatography (HPLC) with turbo-ion spray tandem mass spectometry (LC/MS/MS) with chiral separation. The assay involved alkalinization of the plasma prior to extraction and back-extraction into acid. Following real-

kalinization, the benzoyl derivatives were prepared prior to HPLC with a chiral column.

For *d*- and *l*-AMP, concentrations were linear over the range of 0.5 to 50 ng/mL. A weighted [(1/*x*), where *x* = the concentration of the compound] linear regression was used to determine slopes, intercepts, and correlation coefficients for *d*- and *l*-AMP levels in study samples and quality control samples. PK variables were calculated for plasma drug concentration-time area under the curve ($AUC_{0\text{-}24}$ and $AUC_{0\text{-}inf}$), maximum drug concentration (C_{max}), and time to C_{max} (T_{max}).

Dependent Measures

Primary efficacy variables were the classroom ratings of the Attention and Deportment subscales of the Swanson, Alger, M-Flynn, and Pelham (SKAMP) rating scale and performance on a 10-minute Math Test (number of problems attempted and number of problems solved correctly). These measures have been shown to be drug-sensitive in prior research (Wigal et al., 1998).

In addition, to provide secondary measures of efficacy and side effects, parents were instructed to complete a behavior rating scale at mid-week and a side effect rating scale at the end of each week, and to keep a diary to record adverse events, such as delay of sleep onset. Each week, teachers also completed the Teacher Side Effect Rating Scale. During the analog classroom day, adverse events were noted by study physicians and research staff.

Statistical Analyses

Mean *d*- and *l*-AMP concentrations were measured repeatedly over time for the QD and BID conditions. The PK parameters for each child were calculated on the basis of a noncompartmental modal. The AUC was computed using trapezoidal rule. Analyses were performed to evaluate effects of condition (QD versus BID) on levels of the *d*- and *l*-isomers, as well as on the derived PK parameters. To evaluate PD effects, analysis of variance (ANOVA) was performed using a 2 × 4 design with condition (QD and BID) and time-after-second-dose (0, 1.5, 3.5, and 6.0 hours) as the independent variables and SKAMP ratings of attention and deportment and number of problems attempted and solved correctly as dependent variables.

RESULTS

Patient Demographics

Characteristics of the sample are shown in Table 1. Eleven boys and one girl participated in the study. The mean age of the total sample was 9.8 years (± 1.9). Nine of the patients were Caucasian (75%) and the remainder were Hispanic (25%).

PK Results

The mean plasma concentration profiles for *d*- and *l*-AMP following QD and BID dosing are presented in Table 2. For the QD condition, the average AUC was about three times greater for the *d*-isomer (342.1 ng/h/$mL_{0\text{-}24}$) than the *l*-isomer (124.2 ng/h/$mL_{0\text{-}24}$), which reflects the 3:1 ratio of the isomers in the Adderall formulation. For both isomers, the values of $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max} were significantly higher (approximately twice) for the BID condition compared to the QD condition. The elimination constant (k_e) and the elimination half-life (T½) did not differ significantly for the two conditions.

TABLE 1
Subject Characteristics and Mean Pharmacokinetic Parameters Following 10 mg of Adderall Dosed Once-Daily and Twice-Daily

	Site 1	Site 2	Total
Subject (*n*)	6	6	12
Gender: *n* (%)			
Male	6 (100)	5 (83.3)	11 (92)
Female		1 (16.7)	1 (8.3)
Age (yr)			
Mean (SD)	9.8 (1.7)	9.8 (2.0)	9.8 (1.0)
Range	7.0–12.0	8.0–12.0	8.0–12.0
Weight (lb)			
Mean (SD)	90.5 (29.9)	76.0 (26.9)	83.3 (28.2)
Range	59.0–144.0	55.0–127.0	28.0–144.0

PD Properties of Adderall

For each session across the day, mean SKAMP scores (attention and deportment) are shown in Figure 1 for QD dosing and in Figure 2 for BID dosing. In the BID condition, by 1 hour after the morning dose, the mean deportment rating decreased by 83% (from a baseline of 1.38 to 0.23). The ratings remained low at 2 hours after the morning dose (0.27) but then gradually increased until the second dose was administered at noon, when the mean deportment score was 0.58 (still a 58% decrease from baseline). Across the remainder of the afternoon, the deportment scores showed another gradual decrease and were still low (0.29, a 79% decrease from baseline) at 6 hours after the second dose. In the QD condition, the mean deportment score showed a similar rapid and large (76%) decrease by 1 hour after the morning dose (from a baseline of 1.46 to 0.35), and this trend continued for another hour (0.31). By 3 hours after the morning dose, the deportment ratings showed an increase from the minimum (to 0.58) and a general trend of increasing across the rest of the day, settling at a mean value of 0.77 at 6 hours after the second (placebo) dose (a 47% decrease from baseline).

Instead of evaluating the relative change from baseline, the ANOVA evaluated the difference across the four sessions after the second dose between the two conditions to gauge the additional efficacy in the after-

TABLE 2
Mean Pharmacokinetic Parameters Derived Using a Noncompartmental Model for 10 mg QD Dose of Adderall

	d-Amphetamine		*l*-Amphetamine	
	QD	BID	QD	BID
T_{max} (hours)[a]	2.5 ± 1.2	6.5 ± 0.9	2.5 ± 1.2	6.4 ± 0.7
C_{max} (ng/mL)[a]	28.4 ± 6.5	52.7 ± 16.8	9.6 ± 2.4	17.7 ± 5.2
$AUC_{0\text{-}24}$ (ng/mL)[a]	342.1 ± 108.6	630.6 ± 161.5	124.2 ± 37.2	227.3 ± 65.9
$AUC_{0\text{-}inf}$ (ng/mL)[a]	384.4 ± 108.6	789.3 ± 242.3	146.3 ± 51.6	305.8 ± 112.0
$T_{1/2}$	7.5 ± 1.0	7.8 ± 1.8	8.6 ± 1.6	8.9 ± 2.5
K_e	0.09 ± 0.01	0.09 ± 0.02	0.08 ± 0.02	0.08 ± 0.02

[a] For both isomers, the differences between QD and BID schedules were statistically significant.

noon of the BID condition over the QD condition. In the ANOVA, the average difference for the deportment ratings (0.62–0.40) was statistically significant (p = .0187), and the condition × time interaction was also significant (p = .0038).

Similar effects were seen for the rating of attention, which were expected to be less sensitive for monitoring medication effects (Swanson et al., 1998a). In the BID condition, by 1 hour after the morning dose, the attention ratings had improved by 64% (from a baseline of 0.75 to 0.27). These ratings remained low across the remainder of the morning and the entire afternoon after the second dose (from 0.38 to 0.44, for at least a 45% decrease from baseline). In the QD condition, by 1 hour after the morning dose, the mean attention ratings improved by 54% (from a baseline of 0.83 to 0.38) and continued to improve for the next two morning test sessions (to 0.35 and 0.33) and the first session after the second dose (to 0.21, for a 75% decrease from baseline). However, starting at 6 hours after the morning dose and continuing across the afternoon, the attention ratings showed an increase from the minimum, with mean ratings ranging from 0.52 to 0.58. In the ANOVA of the difference between the QD and BID conditions across the four afternoon sessions, the same trend reported for the deportment ratings was present, but it was not statistically significant (p = .4557).

Mean scores on the math test for the two measures (number attempted and number solved) were highly

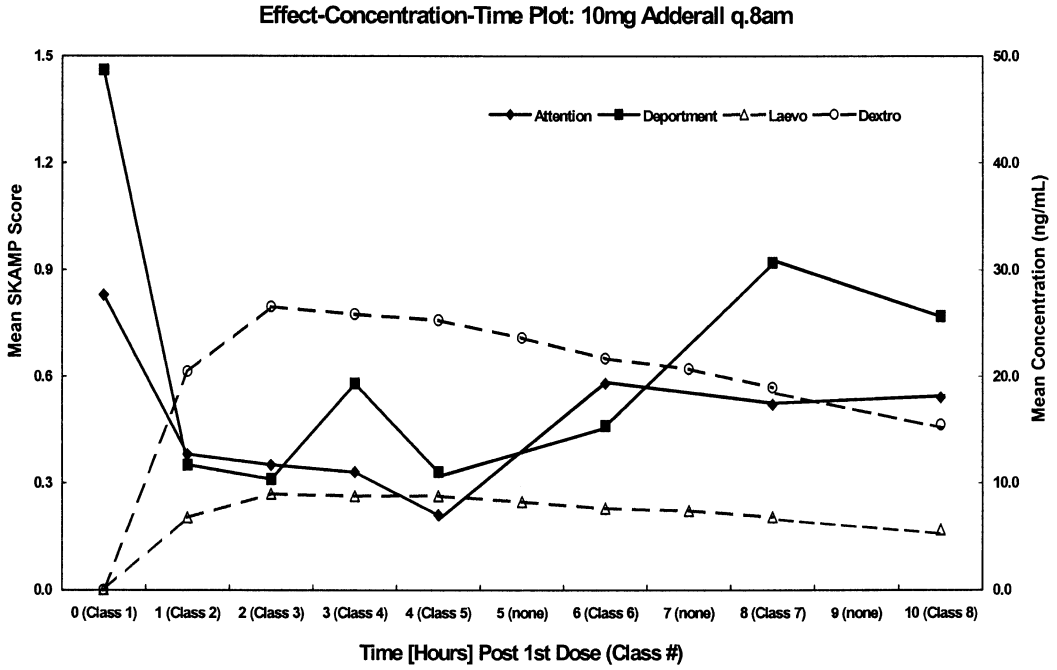

Fig. 1 SKAMP score: pharmacokinetics and pharmacodynamics: 10 mg of Adderall given at 8 A.M.

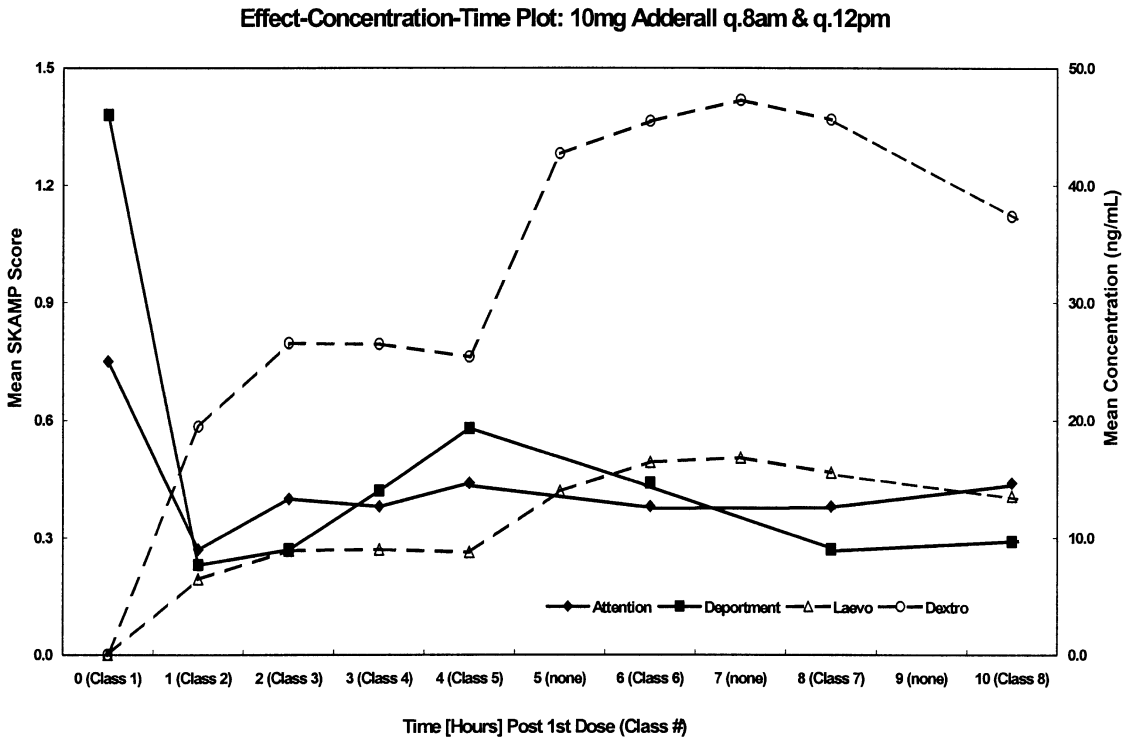

Fig. 2 SKAMP score: pharmacokinetics and pharmacodynamics 10 mg of Adderall given at 8 A.M. and noon.

correlated, so the results for only one (number solved) will be reported. In the BID condition, by 1 hour after the morning dose, the number solved had increased by 23% (from a baseline of 125.9 to 155.3), and this trend continued and reached a maximum of 172.3 (a 37% increase over baseline) at 2 hours after the morning dose. Then performance declined slightly to 158.3. After the noon dose, the increasing trend was reinstated over the afternoon, with a range of scores from 164.2 to 169.9. In the QD condition, a 30% increase from baseline occurred by 1 hour after the morning dose (from 130.1 to 169.2), and this trend continued and reached a maximum (180.3) at 2 hours after the morning dose. Starting at the last morning session before the noon dose and continuing across the remainder of the day, a gradual decrease was observed with a score of 156.8 at 10 hours after the morning dose. In the ANOVA of the difference between the BID and QD conditions, the average performance across the afternoon in the BID condition (166.2) compared to the QD condition (156.5) was statistically significant (p = .0129), but the condition × time interaction was not (p = .7763).

Pearson correlation coefficients based on the concentrations of AMP and the PD measures of efficacy are shown in Table 3. In the QD condition, all correlations were negative for the SKAMP ratings, and they were significant (at $p < .05$) for Attention (–0.344 for the *l*-isomer and –0.344 for the *d*-isomer) and for deportment (–0.526 for the *l*-isomer and –0.528 for the *d*-isomer). In the BID condition, the correlations for attention were negative but not significant (–0.236 for the *l*-isomer and –0.252 for the *d*-isomer), but the correlations for deportment were significant at $p < .05$ (–0.555 for the *d*-isomer and –0.567 for the *l*-isomer). The number of math problems solved increased with increasing plasma concentrations, generating positive and statistically significant (at $p < .05$) correlations for both the QD (0.548) and BID (0.553) conditions.

Adverse Events

Four subjects reported adverse events in the QD condition (one subject had headaches, one had insomnia, one had blurry vision, and one had a bloody nose and diarrhea) and two in the BID condition (one subject complained of tiredness and another complained of stinging around his IV catheter and paresthesias and hit his head on the floor). All adverse events were mild in severity and resolved within the same day. No serious adverse events were reported during the study, and no subjects discontinued because of an adverse event.

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