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Analog Classroom Assessment of a Once-Daily Mixed Amphetamine Formulation, *SLI381 (ADDERALL XR)*, in Children With *ADHD*

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ABSTRACT

Objectives: This investigation was conducted primarily to assess the safety and efficacy of SLI381 (Adderall XR™), developed as a once-daily treatment for children with attention-deficit/hyperactivity disorder (ADHD). Secondary objectives included examination of the time course, pharmacokinetic, and pharmacodynamic properties of SLI381. **Method:** This was a randomized, double-blind, crossover study of three doses of SLI381 (10, 20, and 30 mg), placebo, and an active control (Adderall® 10 mg) given once daily to 51 children with ADHD. Weekly assessments in an analog classroom setting included blind ratings of attention and deportment and a performance measure (math test) obtained every 1.5 hours over a 12-hour period. **Results:** SLI381 was well tolerated. All active treatment conditions displayed significant time course effects and were superior to placebo in improving efficacy measures. Dose-dependent improvements were evident for SLI381. SLI381 20 and 30 mg and Adderall all showed rapid improvements by 1.5 hours, but only the SLI381 20- and 30-mg doses showed continued activity at 10.5 and 12 hours for classroom behavior and math test performance versus placebo. **Conclusions:** These data provide support for the benefit of this novel, once-daily amphetamine preparation in the treatment of ADHD. The longer duration of action of SLI381 has the potential to simplify psychostimulant dosing, thus reducing dose diversion and eliminating the need for in-school administration. SLI381 appears to be a useful treatment option for many children with ADHD. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(6):673–683. **Key Words:** attention-deficit/hyperactivity disorder, amphetamine, Adderall®, ADDERALL XR™, stimulant, children.

Psychostimulant medications comprise a mainstay of treatment for attention-deficit/hyperactivity disorder (ADHD), with a long history of research documenting the acute efficacy of both amphetamine and methylphenidate (Arnold et al., 1978; Barkley, 1990; Bradley, 1950; Connors, 1972; MTA Cooperative Group, 1999; Pelham et al., 1990; Spencer et al., 1996; Swanson et al., 1978; Weiss et al., 1971). However, clinical experience and a variety of research data suggest that there is a continued need to develop strategies to optimize these treatments, especially as they are applied in community practice settings. Specifically, the short duration of action of available stimulants necessitates multiple daily doses for many children to provide effective symptom management (Pelham et al., 1987; Swanson et al., 1978). Some have suggested the brief duration of action may undercut the possible long-term benefit of stimulant treatment (Schachar and Sugarman, 2000). Clinically, children with ADHD often experience difficulty with evening homework requirements and less structured family routines, requiring additional medication later in the day. The complexity of multiple daily dosing schedules contributes to reduced compliance and may increase the likelihood of drug diversion. Both practice patterns and poor compliance also serve to reduce the overall benefit of psychostimulant

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treatment of many children with ADHD (Brown et al., 1987; Kauffman et al., 1981; MTA Cooperative Group, 1999). Therefore, there is a need to develop drug delivery systems that can effectively treat ADHD symptoms with a single daily dose.

In spite of the frequency of use of amphetamine-containing products for the treatment of ADHD, there is a surprising paucity of studies on the pharmacokinetic (PK) and behavioral time course of effects of low-dose amphetamine administration for ADHD (Brown et al., 1979, 1980; Pelham et al., 1999; Swanson et al., 1998). The current study describes the efficacy, tolerability, and detailed time course of SLI381 (Adderall XR™), a unique drug delivery system containing the mixture of amphetamine salts contained in a currently approved treatment, Adderall®, on symptoms of ADHD in a sample of children with ADHD.

Adderall is a racemic mixture of dextro- and levo-isomers of amphetamine composed of equal parts of amphetamine salts (*d*-amphetamine sulfate, *d*-amphetamine saccharate, *d,l*-amphetamine aspartate monohydrate, and *d,l*-amphetamine sulfate). The mixture yields a 3:1 ratio of dextro- to levo-isomers of amphetamine. A previous analog classroom pharmacodynamic study of Adderall documented the time course of behavioral and classroom performance effects across a dose range of 5 to 20 mg given once, with behavioral effects evident up to approximately 5 to 7 hours postdose for the highest dose condition (Swanson et al., 1998). Pelham et al. (1999) studied Adderall effects in a summer treatment program and found apparent benefits up to 7 hours after administration. James et al. (2001) recently described locomotor activity effects of amphetamine preparations up to 12 hours postdose, but they did not repeatedly probe disruptive behavior or academic performance. It is interesting that the Swanson et al. (1998) report also demonstrated the pattern of deterioration on placebo in performance across morning into afternoon assessments, highlighting the importance of providing appropriate control groups for time-response studies.

This study was aimed to systematically evaluate the efficacy and tolerability of SLI381 as a treatment for ADHD, using an analog classroom observational procedure. SLI381 is designed to release two pulses of active medication, modeling the PK profile of Adderall administered twice daily with doses administered approximately 4 hours apart. A 20-mg dose of SLI381 is bioequivalent to Adderall 10 mg b.i.d., with a 4-hour interval (Michaels et al., 2001). In addition, the study adds to the literature on the behavioral and cognitive effects of amphetamines in children with ADHD.

METHOD

The study was conducted at four academic sites under local university human subject protection committee approval. Subjects were recruited at the four sites through a combination of advertising and distribution of information about study participation at local outpatient clinics. All subjects provided written assent for study participation; parents provided written consent for their child's enrollment. Families were compensated $50 for participation in each all-day analog classroom day.

Subjects

Potential subjects were screened to meet the following eligibility criteria: (1) age 6 to 12 years; (2) diagnosis of *DSM-IV* ADHD (combined or hyperactive-impulsive subtype as determined by a comprehensive clinician evaluation and selected modules of the Diagnostic Interview Schedule for Children, Version IV-Lifetime [DISC-IV]) (Shaffer et al., 2000) administered by a research staff member with suitable training; (3) no evidence of mental retardation; and (4) history of positive response to psychostimulant medication, or no prior stimulant treatment. Information pertaining to co-occurring psychopathology from the clinical evaluation was supplemented by the Comorbid Disorders Checklist (Hudziak et al., 1993), a parent-report questionnaire composed of *DSM-III-R* symptom items. All diagnoses were based on *DSM-IV* criteria. Subjects were excluded if they met criteria for any of the following: (1) comorbid psychiatric conditions including psychosis, pervasive developmental disorder, bipolar disorder; (2) severe obsessive-compulsive disorder, severe depressive or anxiety disorder (severe defined as any comorbid disorder with impairment necessitating concurrent treatment of any type); (3) a clinically significant medical condition (e.g., seizure disorder, hypertension, abnormal laboratory test result); (4) need for ongoing medical treatment; (5) intolerance of psychostimulants; (6) history of nonresponse to Adderall; or (7) history of a tic disorder. A total of 51 subjects met all eligibility criteria and provided consent for participation. The characteristics of the sample are listed in Table 1.

Study Design

Following screening and a 1-week washout period with discontinuation of previous stimulant medication, 51 eligible subjects were enrolled and assessed in an analog classroom setting on 7 consecutive Saturdays. The first prerandomization study day involved the open-label administration of 20 mg of SLI381 to all subjects with repeated plasma sampling for PK analyses to assess individual tolerability to the drug, to acquire data on SLI381's PK profile, and to familiarize subjects with the research environment and procedures. The study design which followed the first study day was randomized, double-blind, crossover, placebo- and active-controlled. Subjects who tolerated the initial study day and exposure to SLI381 were then randomly assigned in a crossover design to each of five treatment weeks: SLI381 10 mg (equivalent to Adderall 5 mg b.i.d. with a 4-hour dosing interval), SLI381 20 mg (equivalent to Adderall 10 mg b.i.d.), SLI381 30 mg (equivalent to Adderall 15 mg b.i.d.), Adderall 10 mg, and placebo, each administered daily at 7:30 A.M. A Latin square design was used to determine the randomization sequence for individual subjects for the first 5 weeks with approximately one fifth of the sample randomized to each of five treatment sequences. Randomization schedules

TABLE 1
Demographic and Baseline Characteristics of Randomized Sample

Characteristic	All Patients (N = 51)
Gender: *n* (%)	
Male	44 (86.3)
Female	7 (13.7)
Race: *n* (%)	
White	25 (49.0)
Black	8 (15.7)
Hispanic	12 (23.5)
Asian/Pacific Islander	3 (5.9)
Other	3 (5.9)
Age (yr): mean ± SD	9.5 ± 1.9
Weight (lb): mean ± SD	83.5 ± 28.9
Height (in): mean ± SD	54.6 ± 4.9
ADHD diagnosis: *n* (%)	
Hyperactive-impulsive	1 (2.0)
Combined	50 (98.0)
Duration of prior stimulant treatment: mean ± SD (yr)	1.7 ± 1.7
ADHD treatment before study entry: *n* (%)	
Amphetamine only	17 (33.3)
Methylphenidate only	30 (58.8)
None listed	4 (7.8)

Note: ADHD = attention-deficit/hyperactivity disorder.

were generated by the sponsor of the study and distributed to the on-site research pharmacists. A sixth treatment week was included as a potential makeup week and as a week for additional PK sampling across all treatment groups, and treatment assignment was handled by a separate procedure. Those subjects who had not completed one of the five randomly assigned treatment conditions were assigned to the missed condition during the final week; those subjects who had completed all prior treatment weeks were randomly assigned to repeat one of the five treatment conditions. All subjects were invited to return for the final analog classroom session. During the final analog classroom day of the makeup week, PK sampling was again performed on all subjects.

Pharmacokinetic Sampling

When a subject arrived at the laboratory for study visits 1 and 7, an indwelling catheter was inserted into an antecubital vein for plasma sampling. PK samples were obtained at predose, 0.5, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, and 24 hours after administration of SLI381. Concentrations of *d*- and *l*-amphetamine were assayed using validated liquid chromatography-mass spectroscopy methodology at a central laboratory. Results of the PK analyses will be presented in a separate report.

Analog Classroom Protocol

Subjects were assessed in groups of children during consecutive analog classroom study days held on Saturdays at each site. The schedule and procedures for the analog classroom days were based on a modification of well-validated procedures used in previous time-response stimulant studies (Pelham et al., 1995; Swanson et al., 1978, 1998, 2000). On each classroom day, subjects were instructed to arrive at the laboratory at approximately 7:00 A.M.; they remained until 7:30 or 8:00 P.M. All subjects were administered study material capsules by study physicians at 7:30 A.M. The daily schedule consisted of alternating classroom, play, meals or snacks, and research activities, with a classroom period scheduled every 1.5 hours, beginning immediately after morning dose administration and recurring at 1.5, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0 hours after administration. To allow extra recess time for study subjects, no classroom (efficacy assessment) period was scheduled at 3.0 hours. Each classroom period lasted a total of 45 minutes and was directed by two teachers for the group of 10 to 15 subjects. In addition, each classroom contained two observers who simultaneously rated the behaviors of one half of the study group, using a behavioral observation system described previously (Swanson et al., 1998, 2000). All classroom raters had completed reliability training for behavioral assessments. Outside of the classroom period, a separate group of research staff (counselors) directed and supervised subjects' activities. To avoid confounding observation of medication effects, no behavioral or other treatment approaches were used during the analog classroom days.

Dependent Measures

Several primary and secondary efficacy measures were obtained during the study. Primary efficacy variables included the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale Attention and Deportment variables (Swanson et al., 2000), as completed by the classroom raters during each classroom period. Test-retest reliability and concurrent validity of the SKAMP are high (Wigal et al., 1998). In addition, academic performance was assessed using a Permanent Product Measure of Performance (PERMP), a 10-minute age-appropriate math test that was scored to yield absolute number of problems attempted and problems correct (Swanson et al., 2000). These measures have been shown to be sensitive to both dosage and time effects in prior stimulant research (Swanson et al., 1998).

Secondary measures included a global behavior rating scale (Parent Global Assessment) that parents were instructed to complete at midweek during each of the six treatment weeks. Parents also completed a weekly Side Effect Rating Scale specific to stimulant treatment. Each analog classroom day, teachers completed the Teacher Side Effect Rating Scale and adverse events were noted by study physicians or research staff.

Data Analysis

Statistical analyses were conducted on the primary efficacy variables using a mixed-effects analysis of variance (ANOVA) model, with fixed-effect terms of treatment (placebo, SLI381 10, 20, 30 mg, and Adderall 10 mg), period (weeks 1 through 5), session (0.5, 1.5, 4.5, 6, 7.5, 9, 10.5, 12 hours postdose), and treatment-by-session interaction. In those cases in which the overall treatment-by-session effect was significant ($p < .05$), additional comparisons of individual treatments versus placebo were performed with pairwise comparisons of individual means. As no evidence for possible carryover effects were noted (which would reduce drug-placebo or dose-dependent improvements), no secondary analyses for carryover effects were performed. All p values reported are two-tailed.

RESULTS

Fifty-one children were enrolled in the study. The mean age of the total sample was 9.5 (±1.9) years. The sample consisted of 44 boys and 7 girls. The subjects had a mean duration of prior psychostimulant medication treatment of 1.7 (±1.7) years. Of those children with a history of

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