SLI381 (Adderall XR), a Two-Component, Extended-Release Formulation of Mixed Amphetamine Salts: Bioavailability of Three Test Formulations and Comparison of Fasted, Fed, and Sprinkled Administration

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Study Objectives. To assess the bioavailability of three test formulations of a single dose of extended-release Adderall 20-mg capsules compared with two doses of immediate-release Adderall 10-mg tablets, and to assess the bioequivalence of a single 30-mg dose of the chosen extended-release Adderall formulation (designated as SLI381) administered in applesauce (sprinkled) and the same dose administered as an intact capsule with or without food.

Design. Randomized, open-label, crossover study.

Setting. Clinical research unit.

Patients. Forty-one healthy adults.

Interventions. Study A had four treatment sequences: three test formulations (A, B, and C) of a single dose of extended-release Adderall 20 mg, and two 10-mg doses of Adderall given 4 hours apart. Study B had three treatment sequences: a single dose of SLI381 30 mg as an intact capsule after overnight fast, an intact capsule after a high-fat breakfast, and the contents of a capsule sprinkled in 1 tablespoon of applesauce.

Measurements and Main Results. The 20-mg test formulation A had comparable pharmacokinetic profiles and bioequivalence in rate and extent of drug absorption to Adderall 10 mg twice/day for both d- and l-amphetamine. Formulations B and C had statistically significant differences from the reference drug in some pharmacokinetic parameters. A 30-mg dose of SLI381 showed no significant differences in rate and extent of absorption of d- and l-amphetamine for fasted or sprinkled conditions compared with the high-fat meal condition.

Conclusion. SLI381 20 mg/day is bioequivalent to Adderall 10 mg twice/day. SLI381 30 mg administered in applesauce is bioequivalent in terms of both rate and extent of absorption to the same dose administered as an intact capsule in both fasted and fed states.

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Attention-deficit–hyperactivity disorder (ADHD) is a neurobehavioral condition characterized by various degrees of developmentally inappropriate inattention, hyperactivity, and impulsivity.[1] It is diagnosed most commonly in childhood, and prevalence rates vary from 4–12% in school-age children.[2] In addition, 50–65% of children with ADHD continue to display behavioral problems and symptoms into their adult lives. The disorder is associated with considerable disability, and the negative impact can be felt not only in academic and vocational

settings, but also in social situations and recreational activities.[3–5] Psychostimulant agents (methylphenidate, amphetamine) are well tolerated and effective in treating core symptoms of ADHD.[6–8] However, therapy can be problematic because of the need for several daily doses in most individuals, which can lead to poor compliance and decreased satisfaction with treatment. In-school dosing in children may lead to diversion of drug, ridicule by peers, and negative impact on self-esteem. Thus, a more effective once-daily dosage form of stimulant drugs that lasts throughout the school day and into the evening is necessary.

Amphetamine compounds and other psychostimulants are first-line treatments for ADHD. Although the precise mechanism of action is not fully elucidated, the agents both accentuate release and block reuptake of neurotransmitters dopamine and norepinephrine in presynaptic neurons.[9] The pharmacokinetic and pharmacodynamic effects of amphetamine are described in adults[10, 11] and children.[12, 13] Amphetamine's absorption is rapid and complete from the gastrointestinal tract, and maximum plasma concentrations are reached in 3–4 hours. The agent undergoes hepatic metabolism by side-chain deamination and ring hydroxylation; most is excreted unchanged in urine.[14] Clinical behavioral effects are most apparent during the absorption phase and decrease after peak plasma concentrations are reached.[10–13] Food has little effect on plasma amphetamine levels, although gastrointestinal acidifying agents (e.g., ascorbic acid) may lower absorption and decrease bioavailability.

Adderall (Shire US Inc., Florence, KY) is a mixture of neutral salts of dextroamphetamine sulfate, amphetamine sulfate, the dextro isomer of amphetamine saccharate, and d, l-amphetamine aspartate. For each Adderall tablet, the combination of salts and isomers results in a 3:1 ratio of dextroamphetamine:levoamphetamine. The efficacy and tolerability of this product in treating children and adults with ADHD were proven in clinical trials.[15–21]

Historically, the efficacy of Adderall was attributed to the chemical composition of d- and l-amphetamine salts. Several small studies in the 1970s explored different effects of d- versus l-amphetamine in children with ADHD.[22–24] The results indicated that both isomers are pharmacologically active and efficacious, with most children responding well to either isomer. However, some children responded only to the d- and some only to the l- isomer. No further investigations have evaluated the different pharmacodynamic activity of the isomers.

SLI381 (Adderall XR; Shire US Inc.) is a new extended-release capsule for treatment of ADHD designed to produce a therapeutic effect that lasts throughout the day, with one morning dose. The capsule contains the same active ingredients as immediate-release Adderall and is composed of two types of beads combined in a 50:50 ratio. Immediate-release beads are designed to release drug content in a time course similar to Adderall. Delayed-release beads are designed to release drug content approximately 4 hours after administration. With the delayed-release component, the capsule, taken once/day, is expected to produce similar pharmacokinetic and pharmacodynamic effects to immediate-release Adderall taken twice/day.

We conducted two studies to address several issues. The primary objective of the first trial (study A) was to assess the bioavailability of a single dose of three different test formulations of extended-release Adderall 20-mg capsules compared with two Adderall 10-mg immediate-release tablets administered 4 hours apart to determine the optimal formulation to take into final development. The purpose of the second trial (study B) was to assess whether the contents of a single 30-mg dose of the chosen extended-release Adderall capsule formulation (SLI381) administered in applesauce is bioequivalent to the same dose administered as an intact capsule with or without food, and to determine the effect, if any, on bioavailability of a single dose of a SLI381 30-mg capsule administered with a high-fat breakfast compared with the same dose administered in the fasted state.

Methods

Subjects

All subjects were screened within 21 days of

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enrollment into either study. Men and women between 18 and 55 years of age with no clinically significant abnormal findings on physical examination, medical history, and clinical laboratory tests during screening were enrolled. Body weight was not to be more than 10% above or below ideal weight for height and estimated frame adapted from 1983 Metropolitan Life Insurance tables.

Major exclusion criteria were treatment with any known cytochrome P450 enzyme–altering agents (e.g., barbiturates, phenothiazines, cimetidine) within 30 days before or during the study; use of any prescription drug within 14 days before or during the study (hormonal contraceptive and hormone replacement therapy for women were allowed); use of any over-the-counter agent within 7 days before or during the study; pregnancy or lactation; positive urine screen for alcohol or drugs of abuse; history of allergic or adverse response to amphetamine or any related drug; history of drug or alcohol abuse; history of clinically significant gastrointestinal tract, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease; and any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or affect the validity of study results.

Subjects were restricted from food or beverages containing alcohol, caffeine, or any xanthine-containing product 48 hours before and during each period of confinement, fruit juices (including grapefruit juice) containing ascorbic acid during confinement, strenuous exercise during confinement, and lying down for the first 4 hours after drug administration to ensure proper stomach emptying.

All subjects gave written informed consent, and the studies were approved by the institutional review board of MDS Harris, Lincoln, Nebraska. All study drugs were supplied by Shire Pharmaceutical Development Inc.

Determination of Sample Size

Findings from previous studies of Adderall and SLI381 delayed-release pellets[25] indicated that the estimate of area under the curve (AUC) test:reference ratio was within 0.90–1.10 for d-amphetamine, and the estimated within-subject–between-formulation σ (log scale) was less than 0.10. Given that the true AUC mean for a test formulation is within the 90% region of the reference, for a sample of 16 subjects, the proposed crossover design would have at least 80% power to reject the null hypothesis of bioinequivalence at the 0.05 level. Based on the assumptions, we planned to enroll 20 and 21 subjects, without replacement, in studies A and B, respectively.

Study A Design

The prototype formulation assessment was a four-way, open-label, crossover design in 20 healthy subjects with 5 subjects/sequence. A standard 4 x 4 Latin square was used to assign subjects to treatments. In each sequence, subjects were given a single 20-mg dose of one of the test products (extended-release Adderall formulation A, B, or C) or two 10-mg doses of the reference drug (Adderall) administered 4 hours apart . Subjects received the other dosing conditions in subsequent study periods according to the randomization scheme. A 7-day washout period separated each treatment.

A 20-mg dose was selected to enable quantification of anticipated blood levels of d- and l-amphetamine over the 48-hour time period analyzed. Experience suggests this dose is often used in clinical practice and would be well tolerated by healthy subjects.

Drug Administration

Subjects were admitted to the clinic in the evening, approximately 12 hours before the scheduled dose. At each treatment period check-in, they completed a brief written questionnaire to affirm that exclusion criteria and restrictions had not been violated since the screening or previous confinement period. In addition, a urine sample was collected to test for alcohol and drugs of abuse, and a blood sample was collected from women for a serum pregnancy test. Subjects remained at the clinic until completion of the 24-hour postdose blood collection and returned to the clinic for 36- and 48-hour postdose specimen collections. After check-in, each subject received an evening snack. On the next day, they consumed a standard high-fat breakfast approximately 20 minutes before drug administration. The breakfast consisted of one English muffin with butter, one fried egg, one slice of American cheese, one slice of Canadian bacon, one 2-oz serving of hash-brown potatoes, and 8 fluid oz whole milk. Water was allowed ad libitum during the study, except for 1 hour before and 2 hours after dosing.

The study drug (a single dose of extended-release Adderall 20 mg as test capsule formulations A, B, or C, or a single dose of Adderall 10 mg) was administered within 5 minutes of meal completion with 8 fluid oz room-temperature tap water. A mouth check was performed after dosing to ensure that the capsule was swallowed. A second single dose of Adderall 10 mg was administered 4 hours later, during lunch, for subjects who were assigned to Adderall treatment. A standard meal schedule was begun with lunch, dinner, and an evening snack. The same menu and meal schedule were administered uniformly for all subjects and for all treatment periods.

Blood Collection

Beginning on each dosing day, 17 blood samples (7 ml/sample) were collected through the 48-hour postdose interval during each study period to determine plasma concentrations of d- and l-amphetamine. Samples were collected by venipuncture into tubes containing ethylenediaminetetraacetic acid and stored on ice before plasma was separated by centrifugation (approximately 2500 rpm x 15 min at 4°C). Plasma samples were frozen and stored at -20°C until assayed. Blood was collected 5 minutes before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, and 48 hours. In addition, 15 ml of blood was collected for the screening clinical laboratory evaluation. For women, another 5 ml/check-in period was collected to test for pregnancy.

Safety Evaluations

Adverse event data were obtained by observation and by unsolicited reporting before, during, and after each dosing and collection phase. Blood pressure and pulse were measured at screening and four other times (immediately before the dose, and 2, 4, and 24 hrs after the dose) on the dosing day of each treatment period.

Analytical Methods

Plasma samples were analyzed by validated procedures.[26] Amphetamine isomers and deuterated analogs as internal standards were extracted from plasma under alkaline conditions into organic solvent. Analytes were back-extracted into acid, made alkaline again, derivatized with benzoyl chloride, and reextracted into organic solvent. After aqueous wash to remove excess reagent, the organic extract was evaporated to dryness and reconstituted in mobile phase. Analysis was performed by chiral high-performance liquid chromatography with turbo-ionspray tandem mass spectrometry detection. A weighted [(1/x) where x = concentration of the compound] linear regression was used to determine slopes, intercepts, and correlation coefficients for d- and l-amphetamine concentrations in study samples and internal standards. For d- and l-amphetamine, concentrations were linear over 0.5–50 ng/ml with a limit of quantification of 0.5 ng/ml. Coefficients of variation were less than or equal to 5.28% for l- and 4.71% for d-amphetamine.

Pharmacokinetic Analysis

Pharmacokinetic parameters were determined for bioavailability and bioequivalence evaluations for each type of dosing for d- and l-amphetamine by standard noncompartmental methods. The primary pharmacokinetic parameters were area under the drug concentration–time curve from time zero to t hour (AUC_{0-t}), with t the last time point over the time interval with a measurable drug concentration; area under the drug concentration–time curve from time zero to infinity ($AUC_{0-\infty}$); elimination half-life; maximum observed drug concentration (C_{max}); and time to C_{max} (T_{max}). For both isomers, AUC_{0-t} was calculated by the linear trapezoidal rule. The residual AUC between the last time point measured and infinity ($AUC_{t-\infty}$) was determined and added to AUC_{0-t} to obtain $AUC_{0-\infty}$. The $AUC_{t-\infty} = C_t/k_e$, where C_t was the last measurable plasma concentration and k_e was the terminal elimination rate constant determined by linear regression of the terminal log linear phase of the plasma drug concentration-time curve. The half-life for each isomer equalled $0.693/k_e$.

Statistical Analysis

Descriptive statistics (N, mean, SD) of d- and l-amphetamine were obtained for all pharmacokinetic parameters based on the intent-to-treat population. Standard analysis of variance (ANOVA) model of a 4-way crossover design with a general linear approach was applied to AUC, C_{max}, and T_{max} to determine differences among the formulations. The model included sequence, patient-within-sequence, period, and formulation. The sequence effect was tested using the patient-within-sequence effect, and all other effects were tested using the residual error

of the model. For each parameter, mean values of the formulations were compared with the reference formulation (Adderall 10 mg twice/day) using Dunnett's test with the type I error rate of 0.05. The AUC and C_{max} were further analyzed on a log scale to assess bioequivalence of each test formulation and the reference formulation. The recommended two one-sided *t* test hypotheses for average bioequivalence were tested at the 0.05 level by constructing the 90% confidence interval (CI) of the ratio of the test:reference means.[27] Adverse events, blood pressure, and pulse were tabulated descriptively and compared with a paired *t* test.

Study B Design

This trial had a three-way, open-label, crossover design. Twenty-one healthy men and women were randomized to one of the three dose administration sequences with seven subjects/sequence. They were given a single 30-mg dose of the chosen extended-release Adderall formulation (test formulation A from study A)—designated as SLI381—under one of three drug dosing conditions: an intact 30-mg capsule after an overnight fast, an intact 30-mg capsule after a high-fat breakfast, or the contents of a 30-mg capsule sprinkled in 1 tablespoon of applesauce. Subjects received alternate dosing conditions in subsequent periods according to the randomization scheme. A 7-day washout period separated each treatment.

A 30-mg dose was selected to enable quantification of anticipated blood levels of d- and l-amphetamine over the 60-hour period. It also was the highest strength marketed for immediate-release Adderall tablets. Experience suggested this dose would be well tolerated by healthy subjects.

Drug Administration

Subjects were admitted to the clinic in the evening, at least 10 hours before the scheduled dose and followed a protocol identical to that for study A.

On the next day, subjects in the high-fat fed condition received a standard high-fat breakfast approximately 30 minutes before drug administration as described for study A and completed the meal 5 minutes before dosing. For this condition and the fasted condition, the study drug, a single intact capsule of SLI381 30 mg, was administered with 8 fluid oz room-temperature tap water. For subjects receiving the study drug sprinkled on applesauce, a single capsule of SLI381 30 mg was opened and sprinkled into 1 tablespoon of applesauce. A mouth check was performed after dosing to ensure that the dose was swallowed. After administration, subjects were required to fast for 4 hours. Water was allowed ad libitum during the study, except for 1 hour before and 2 hours after dosing. A standard meal schedule was begun with lunch, dinner, and evening snack. The same menu and meal schedule were administered uniformly for all subjects and for all treatment periods. Subjects were monitored for adverse events for the entire study as described for study A.

Blood Collection

Samples (7 ml) of venous blood were collected and processed as in study A, with the addition of 11-hour and 60-hour postdose samples. Analytic methods and pharmacokinetic parameters were determined as described for study A.

Statistical Analysis

Descriptive statistics of d- and l-amphetamine were obtained for all pharmacokinetic parameters based on the intent-to-treat population. An ANOVA model of a 3-way crossover design with a general linear approach was applied to AUC, C_{max}, and T_{max} to determine differences among the conditions. The model included sequence, patient-within-sequence, period, and condition. The sequence effect was tested using the patient-within-sequence effect, and all other effects were tested using the residual error of the model. For each parameter, mean values of fasted and sprinkled conditions were compared with the fed condition using Dunnett's test with the type I error rate of 0.05. The AUC and C_{max} were further analyzed on a log scale to assess bioequivalence between each pair of dosing conditions.[27] Adverse events, blood pressure, and pulse were tabulated descriptively and compared by a paired *t* test.

Results

Study A

Twenty subjects (mean age 40.4 yrs) were enrolled and randomized to treatment (Table 1). Nineteen subjects completed the study; one was withdrawn before dosing in the fourth dosing period as a result of a positive drug test for opiates at check-in. This subject received the

Table 1. Subject Demographics and Baseline Characteristics

Variable	Study A (n=20)	Study B (n=21)
M/F, no. (%)	13/7 (65/35)	11/10 (52/48)
Age, yrs, mean (range)	40.4 (23–55)	35 (20–53)
Race, no. (%)		
Caucasian	17 (85)	17 (81)
Black	2 (10)	2 (9)
Asian	1 (5)	0
Hispanic	0	1 (5)
Native American	0	1 (5)
Height, in., mean (range)	69.8 (63.5–76.0)	67.9 (60.0–74.0)
Weight, lbs, mean (range)	167.8 (122.0–226.0)	162.0 (110.0–203.0)

Table 2. Pharmacokinetic Parameters for d- and l-Amphetamine (Study A)

Formulation	Pharmacokinetic Parameter				
	$AUC_{0-\infty}$ (ng•hr/ml)	AUC_{0-t} (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hrs)	Half-life (hrs)
d-Amphetamine					
Test A 20 mg q.d. (SLI381)	566.62 ± 114.30	522.47 ± 100.72	28.13 ± 8.84	6.95 ± 2.35	11.83 ± 2.74
Test B 20 mg q.d.	473.83[a] ± 114.46	426.24[a] ± 95.37	18.51[a] ± 4.76	5.60 ± 2.56	13.87[a] ± 3.29
Test C 20 mg q.d.	546.76 ± 126.02	496.68 ± 101.75	22.86[a] ± 5.85	9.37[a] ± 3.02	12.21 ± 2.97
Adderall 10 mg b.i.d. (reference)	529.92 ± 114.44	494.63 ± 103.10	28.33 ± 7.13	6.90 ± 1.25	10.90 ± 2.04
l-Amphetamine					
Test A 20 mg q.d. (SLI381)	203.12 ± 46.04	178.28 ± 40.44	8.67 ± 2.80	8.15 ± 4.44	13.72 ± 2.83
Test B 20 mg q.d.	169.34[a] ± 46.56	144.70[a] ± 36.41	5.75[a] ± 1.56	5.70 ± 2.62	15.78[a] ± 3.61
Test C 20 mg q.d.	197.47 ± 49.85	168.97 ± 39.86	7.16[a] ± 1.95	9.74[a] ± 3.21	14.70 ± 3.63
Adderall 10 mg b.i.d. (reference)	202.67 ± 49.05	180.83 ± 41.96	9.25 ± 2.41	7.10 ± 1.37	13.19 ± 2.69

Data are mean ± SD.
$AUC_{0-\infty}$ = area under the drug concentration-time curve from time zero to infinity; AUC_{0-t} = AUC from time zero to t hour; C_{max} = maximum observed drug concentration; T_{max} = time to C_{max}.
[a]$p<0.05$ compared with reference by Dunnett's test.

assigned treatments of test formulations A, B, and Adderall in periods 1, 2, and 3, respectively. All information collected from this subject was included in the analyses.

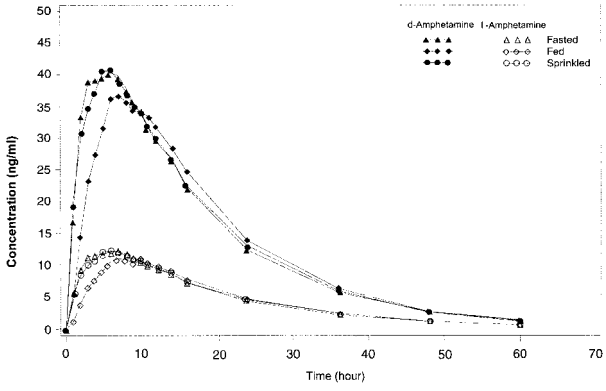

Figure 1. Mean plasma d- and l-amphetamine concentration versus time profiles for single 20-mg doses of test formulations A, B, and C, and immediate-release Adderall 10 mg twice/day with a 4-hour interval.

Pharmacokinetic Parameters

Mean plasma concentrations versus time profiles of d- and l-amphetamine after drug administration are shown in Figure 1. Table 2 gives descriptive statistics of pharmacokinetic parameters for each formulation. The ANOVA results of the 4-way crossover indicate statistically significant differences among the four formulations in $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, and T_{max}. In reference to Adderall, multiple means comparisons by Dunnett's test disclosed statistically significant ($p<0.05$) differences in $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for test formulation B; statistically significant ($p<0.05$) differences in C_{max} and T_{max} for test formulation C; and no statistically significant differences in these parameters for test formulation A. These observations held for both isomers.

Table 3 shows bioequivalence results on logarithmic transformations of pharmacokinetic

Table 3. Bioequivalence of Pharmacokinetic Parameters (Study A)

Formulation	Test:Reference Ratio[a] (90% confidence interval)		
	$AUC_{0-\infty}$	AUC_{0-t}	C_{max}
d-Amphetamine			
Test A (SLI381)	1.07 (1.02–1.13)[b]	1.06 (1.01–1.11)[b]	0.97 (0.92–1.04)[b]
Test B	0.90 (0.86–0.95)[b]	0.86 (0.82–0.90)[b]	0.65 (0.61–0.70)
Test C	1.06 (1.01–1.11)[b]	1.02 (0.97–1.06)[b]	0.82 (0.77–0.88)
l-Amphetamine			
Test A (SLI381)	1.01 (0.95–1.07)[b]	0.99 (0.94–1.04)[b]	0.92 (0.86–0.98)[b]
Test B	0.84 (0.79–0.89)	0.80 (0.76–0.84)	0.62 (0.58–0.66)
Test C	1.00 (0.94–1.06)[b]	0.95 (0.90–1.00)[b]	0.79 (0.74–0.84)

$AUC_{0-\infty}$ = area under the drug concentration-time curve from time zero to infinity; AUC_{0-t} = AUC from time zero to t hour; C_{max} = maximum observed drug concentration.
[a]Immediate-release Adderall administered twice/day.
[b]The 90% confidence interval falls within the 0.80–1.25 limits of bioequivalence when analyzed on a logarithmic scale.

data. The 90% CIs of the test:reference ratio fell within the 0.80–1.25 limits of average bioequivalence for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for test formulation A for d- and l-amphetamine. Test formulation B did not fall within the limits on any parameter for l-amphetamine, and for d-amphetamine, fell outside the limits for C_{max}. For d- and l-amphetamine levels, test formulation C did not fall within the limits for C_{max}. Thus, a single 20-mg dose of test formulation A was bioequivalent to Adderall 10 mg twice/day for the two isomers in terms of rate (C_{max}) and extent (AUC) of absorption.

Safety

All formulations were well tolerated. Eight subjects reported a total of 10 adverse events after starting study drugs: headache (4), insomnia (2), pharyngitis (1), rash (1), somnolence (1), and abnormal vision (1). All events were mild and resolved. Four of the 10 events were attributed as related or possibly related to study drug: headache (1), insomnia (2), and abnormal vision (1). The event rate was similar among the four dosing conditions. No subjects withdrew as a result of adverse events and no deaths or other serious events occurred during the study.

Compared with baseline, consistent increases in pulse 2–24 hours after the dose and slight increases in blood pressures 2–4 hours after dose were seen for all treatment conditions. None of these changes was deemed by investigators to be clinically significant.

Study B

Twenty-one subjects (mean age 35 yrs) were enrolled (Table 1). They all received one oral 30-mg dose of test formulation A (SLI381) as an intact capsule in the fed state. Twenty subjects received one 30-mg dose as an intact capsule in the fasting state and received the contents of one 30-mg capsule sprinkled over applesauce. One subject after receiving a single dose withdrew as a result of necessary drug treatment for gout (colchicine, indomethacin). All information collected from this subject was included in the analyses.

Pharmacokinetic Parameters

Mean plasma levels of d- and l-amphetamine are shown in Table 4 and Figure 2. The ANOVA results of the 3-way crossover indicate no statistically significant differences in $AUC_{0-\infty}$, AUC_{0-t}, or half-life for l- or d-amphetamine in the fasted and sprinkled conditions compared with the fed condition. However, quantitatively small but statistically significant differences were noted for T_{max} and C_{max}.

The results of bioequivalence in the fasted and sprinkled conditions compared with the fed condition using logarithmic transformations of pharmacokinetic data (Table 5) indicate that the 90% CIs of the test:reference ratio fell within the 0.80–1.25 limits of average bioequivalence for all three pharmacokinetic parameters ($AUC_{0-\infty}$, AUC_{0-t}, C_{max}) for both d- and l-amphetamine. Also, 90% CIs of the test:reference ratio for the sprinkled versus fasted condition fell within these limits. Thus, according to criteria of average bioequivalence, the extent and rate of drug absorption for a single 30-mg dose of SLI381 were bioequivalent under the three dosing conditions. The T_{max} was approximately

Table 4. Mean Pharmacokinetics for d- and l-Amphetamine After Administration of SLI381 30 mg (Study B)

	Pharmacokinetic Parameter				
Test Condition	$AUC_{0-\infty}$ (ng•hr/ml)	AUC_{0-t} (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hrs)	Half-life (hrs)
d-Amphetamine					
Fasted	851.17 ± 213.51	827.99 ± 201.96	44.33[a] ± 11.10	5.20[a] ± 1.96	10.40 ± 2.31
Sprinkled	855.98 ± 179.68	834.49 ± 175.14	43.51[a] ± 9.61	5.50[a] ± 1.76	10.39 ± 2.05
Fed	822.56 ± 200.18	799.28 ± 190.50	39.70 ± 8.84	7.67 ± 2.31	10.34 ± 1.98
l-Amphetamine					
Fasted	288.59 ± 79.17	271.72 ± 72.23	13.32[a] ± 3.66	5.55[a] ± 2.09	12.71 ± 3.30
Sprinkled	290.38 ± 64.49	274.65 ± 61.30	13.04[a] ± 3.20	5.60[a] ± 1.73	12.73 ± 2.83
Fed	273.56 ± 68.98	258.31 ± 64.36	11.98 ± 2.89	8.33 ± 2.89	12.50 ± 2.56

Data are mean ± SD.
$AUC_{0-\infty}$ = area under the drug concentration-time curve from time zero to infinity; AUC_{0-t} = AUC from time zero to t hour; C_{max} = maximum observed drug concentration; T_{max} = time to C_{max}.
[a]$p<0.05$ compared with fed condition by Dunnett's test.

Table 5. Bioequivalence of Pharmacokinetics for d- and l-Amphetamine (Study B)

Pharmacokinetic		Test Condition	
Parameter	Measures	Fasted	Sprinkled
d-Amphetamine			
$AUC_{0-\infty}$ (ng•hr/ml)	Ratio of test:fed condition (90% CI)	1.04 (0.98–1.10)[a]	1.05 (0.99–1.11)[a]
AUC_{0-t} (ng•hr/ml)	Ratio of test:fed condition (90% CI)	1.04 (0.99–1.10)[a]	1.05 (1.00–1.11)[a]
C_{max} (ng/ml)	Ratio of test:fed condition (90% CI)	1.12 (1.05–1.18)[a]	1.10 (1.04–1.16)[a]
$AUC_{0-\infty}$ (ng•hr/ml)	Ratio of test:fasted condition (90% CI)	—	1.01 (0.96–1.07)[a]
AUC_{0-t} (ng•hr/ml)	Ratio of test:fasted condition (90% CI)	—	1.01 (0.96–1.07)[a]
C_{max} (ng/ml)	Ratio of test:fasted condition (90% CI)	—	0.99 (0.93–1.04)[a]
l-Amphetamine			
$AUC_{0-\infty}$ (ng•hr/ml)	Ratio of test:fed condition (90% CI)	1.05 (0.99–1.13)[a]	1.07 (1.00–1.14)[a]
AUC_{0-t} (ng•hr/ml)	Ratio of test:fed condition (90% CI)	1.05 (0.99–1.12)[a]	1.07 (1.01–1.14)[a]
C_{max} (ng/ml)	Ratio of test:fed condition (90% CI)	1.11 (1.05–1.18)[a]	1.09 (1.03–1.16)[a]
$AUC_{0-\infty}$ (ng•hr/ml)	Ratio of test:fasted condition (90% CI)	—	1.01 (0.95–1.09)[a]
AUC_{0-t} (ng•hr/ml)	Ratio of test:fasted condition (90% CI)	—	1.02 (0.96–1.08)[a]
C_{max} (ng/ml)	Ratio of test:fasted condition (90% CI)	—	0.98 (0.93–1.04)[a]

[a]The 90% confidence interval (CI) fell within the 0.80–1.25 limits of bioequivalence when analyzed on a logarithmic scale.

2 hours longer for the d-isomer and 3 hours longer for the l-isomer in the presence of a high-fat meal.

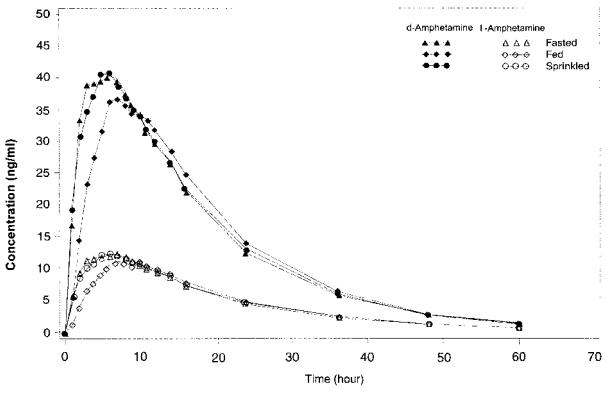

Figure 2. Mean plasma d- and l-amphetamine concentration versus time profiles for a single 30-mg dose of SLI381 administered under three dosing conditions: fasted, after a high-fat meal, and sprinkled in applesauce.

Safety

All formulations were well tolerated. Eleven subjects reported a total of 54 adverse events after the start of dosing, with one subject reporting 18. The events were mild (51) or moderate (3) in severity and resolved or improved. Of the 54 events, 25 were unrelated to study drug and 29 were assessed as related or possibly related to study drug. Most frequently reported were insomnia (7), headache (6), nausea (5), and dizziness (4). The adverse event rate was similar among the three dosing conditions (fasted 14, fed 22, sprinkled 18). No subjects were withdrawn as a result of adverse events, and no deaths or other serious events occurred during the study.

Compared with baseline, a significant increase

in pulse ($p<0.01$) 24 hours after dosing was noted for all three dosing conditions (average change 10–11 beats/min). A significant increase ($p<0.01$) in systolic blood pressure was noted 2 and 4 hours after the dose for the sprinkled condition only. By 24 hours after dosing, mean systolic blood pressures returned to baseline. No significant increases in diastolic blood pressure were noted. No changes in blood pressure or pulse were considered clinically significant by investigators.

Discussion

Other pharmacokinetic studies of d-amphetamine in adults reported time to maximum plasma concentrations to be between 2 and 4 hours for immediate-release formulations.[10, 11] In our study, T_{max} values for SLI381 were between 5 and 8 hours; immediate-release Adderall had a T_{max} of approximately 7 hours after twice-daily dosing. Immediate-release Adderall, however, had a first peak plasma level 3 hours after the first dose, similar to previous studies of a single dose of immediate-release d-amphetamine. SLI381 displayed fairly consistent T_{max} values for d-amphetamine between our studies in the fed condition: study A, 20-mg dose, 6.95 hours; study B, 30-mg dose, 7.67 hours.

The literature examining pharmacokinetic and pharmacodynamic effects of amphetamine in adults[10, 11] and children[12, 13] shows little correlation between serum levels and behavioral effects. In those studies, effects on behavior and learning performance were greatest during the absorption phase and declined slowly thereafter despite substantial amphetamine levels. Clinical experience with Adderall indicates that duration of action increases with increasing dosage,[15] perhaps by extending the absorption phase. However, escalation of a single dose may progress only as far as tolerated; adverse effects can limit the maximum single dose of the immediate-release product. Typical schedules in children with ADHD, in whom several daily doses are required, involve early morning and noon-time doses. The goal in developing an extended-release formulation of Adderall was, through a two-pulse delivery system, to replicate the ascending pharmacokinetic curve attained with twice-daily dosing of Adderall at a 4-hour interval in order to provide all-day coverage of ADHD symptoms with a single daily dose.

In the analysis of raw data, study A showed that extended-release Adderall test formulation A administered as a single 20-mg dose had comparable bioavailability and pharmacokinetic profiles for both d- and l-amphetamine as Adderall 10 mg twice/day. Furthermore, on log transformation of pharmacokinetic data, test formulation A, administered as a single 20-mg capsule, was bioequivalent to two 10-mg doses of Adderall administered 4 hours apart. The smooth ascending pharmacokinetic curve of this formulation significantly mimics that of Adderall twice/day. This formulation was chosen to take into final development and used in clinical trials under the name SLI381; it is marketed as Adderall XR. Further clinical studies with SLI381 in children with ADHD confirmed the onset of action to be rapid (within 1.5 hrs), and behavioral and academic performance was maximum during the absorption phase.[28] The half-life in children was 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine than in adults, consistent with previous reports.[12, 13]

Study B revealed a 30-mg dose administered in applesauce is bioequivalent for both d- and l-amphetamine with the same dose administered as an intact capsule in either high-fat fed or fasting state, with log transformed C_{max} and $AUC_{0-\infty}$ values falling within accepted criteria for 90% CI of 0.80–1.25. In addition, an intact capsule of SLI381 30 mg administered in the fasted state is bioequivalent in terms of rate and extent of absorption for both d- and l-amphetamine with the same dose administered in the high-fat fed state. The T_{max} was, on average, about 2 hours longer for the d-isomer and 3 hours longer for the l-isomer in the presence of food, compared with that of either fasted or sprinkled state. Thus, the absorption of both isomers appears to have been slightly delayed in the presence of food. These observations are consistent with work describing an increase in time for gastric emptying in the presence of food.[29]

Study B further established pharmacokinetic parameters of SLI381 under different dosing conditions. An important result of this study was that the extent of absorption was not significantly affected after administration of a high-fat meal. The bioavailability of this dosage form was not significantly altered when the capsule contents were sprinkled into applesauce. These findings are important clinically because the type and amount of food consumed at breakfast (intended time for dosing of the drug) may vary considerably from person to person and from day

to day. The availability of a once-daily dosage form that allows for this flexibility in administration is especially important for individuals, primarily children, who may have difficulty swallowing capsules.

In both studies, SLI381 was well tolerated. The most common drug-related adverse events (insomnia, headache, nausea) were consistent with frequently reported adverse events with psychostimulant agents, were generally of mild intensity, and quickly resolved. Although it might be anticipated that more gastrointestinal adverse events would be reported under fasted conditions, the findings from study B demonstrated that the fasted and sprinkled conditions elicited comparable rates and types of adverse events to the fed condition. Slight increases in pulse and blood pressure were clinically insignificant under all dosing conditions.

Summary

These studies document the pharmacokinetics of SLI381 (Adderall XR) in healthy adult volunteers. A dose of SLI381 20 mg closely mimics the pharmacokinetics of immediate-release Adderall 10 mg twice/day administered at a 4-hour interval, and the two conditions were bioequivalent with a similar safety profile. This extended-release formulation of Adderall, administered once/day in the morning, is expected to elicit a similar time course of clinical effect as the same total daily dose of immediate-release Adderall given in two divided doses with a 4-hour interval.

An important result was that the extent of absorption of SLI381 was not significantly altered after administration of a high-fat meal, allowing patients the option of taking the capsule with or without food. Finally, sprinkling the capsule contents into applesauce was equivalent in the rate and extent of absorption to taking the capsule whole, with or without food, providing further dosing flexibility for patients who have difficulty swallowing capsules.

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