

Relative Bioavailabilities of Lisdexamfetamine Dimesylate and D-Amphetamine in Healthy Adults in an Open-Label, Randomized, Crossover Study After Mixing Lisdexamfetamine Dimesylate With Food or Drink

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Background: This open-label, crossover study examined lisdexamfetamine dimesylate (LDX) and D-amphetamine pharmacokinetics in healthy adults after administration of an intact LDX capsule or after the capsule was emptied into orange juice or yogurt and the contents consumed.

Methods: Healthy adult volunteers (N = 30) were administered a 70-mg LDX capsule or the contents of a 70-mg capsule mixed with yogurt or orange juice using a 3-way crossover design. Blood samples were collected serially for up to 96 hours after dose. Pharmacokinetic endpoints included maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) or to last assessment (AUC_{last}). Relative LDX and D-amphetamine bioavailabilities from the contents of a 70-mg LDX capsule mixed with orange juice or yogurt were compared with those from the intact LDX capsule using bioequivalence-testing procedures.

Results: Geometric least squares mean ratios (90% confidence intervals [CIs]) for D-amphetamine (active moiety) were within the prespecified bioequivalence range (0.80–1.25) when the contents of a 70-mg LDX capsule were mixed with orange juice [C_{max} : 0.971 (0.945, 0.998); $AUC_{0-\infty}$: 0.986 (0.955, 1.019); AUC_{last} : 0.970 (0.937, 1.004)] or yogurt [C_{max} : 0.970 (0.944, 0.997); $AUC_{0-\infty}$: 0.945 (0.915, 0.976); AUC_{last} : 0.944 (0.912, 0.977)]. Geometric least squares mean ratios (90% CIs) for LDX (inactive prodrug) were below the accepted range when the contents of a 70-mg LDX capsule were mixed with orange juice [C_{max} : 0.641 (0.582, 0.707); $AUC_{0-\infty}$: 0.716 (0.647, 0.792); AUC_{last} : 0.708 (0.655, 0.766)]; the lower 90% CI for C_{max} [0.828 (0.752, 0.912)] was below the

accepted range when the contents of a 70-mg LDX capsule were mixed with yogurt.

Conclusions: Relative bioavailability of D-amphetamine (the active moiety) did not differ across administrations, which suggests that emptying an LDX capsule into orange juice or yogurt and consuming it is an alternative to intact capsules.

Key Words: D-amphetamine, lisdexamfetamine, pharmacokinetics, yogurt, orange juice

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INTRODUCTION

Lisdexamfetamine dimesylate (LDX), a prodrug of D-amphetamine,¹ is approved in the United States and other countries for use in patients aged 6 years and older with attention-deficit/hyperactivity disorder (ADHD) and only in the United States for adults with moderate to severe binge eating disorder.² The pharmacokinetic profiles of orally administered LDX and its active metabolite, D-amphetamine, have been examined in several studies.^{3–7} In 2 studies, after administration of a single 70-mg LDX dose to healthy adults under fasting conditions, which were initiated 10–11 hours before dose, D-amphetamine mean maximum plasma concentration (C_{max}) ranged from approximately 70 to 80 ng/mL, area under the plasma concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) ranged from 1110 to 1342 ng·h⁻¹·mL⁻¹, mean time to maximum concentration (t_{max}) ranged from 3 to 4 hours, and terminal half-life ($t_{1/2}$) ranged from 9.7 to 10.4 hours.^{3,5} In another study, mean C_{max} and $AUC_{0-\infty}$ for D-amphetamine in healthy adults under fasting conditions, which were initiated 10 hours before dose, increased dose-proportionally as the LDX dosage increased from 50 to 250 mg, with mean values ranging from approximately 45 ng/mL and 818 ng·h⁻¹·mL⁻¹, respectively, after 50-mg LDX and to 246 ng/mL and 5133 ng·h⁻¹·mL⁻¹ after 250-mg LDX.⁴ In a fourth study, after 7 days of 70-mg LDX in adults, the mean steady-state C_{max} and $AUC_{0-\infty}$ levels for D-amphetamine were 90 ng/mL and 1110 ng·h⁻¹·mL⁻¹, respectively, with an average observed D-amphetamine concentration of approximately 46 ng/mL.⁶ Finally, in children with ADHD, under fasting conditions, which were initiated at

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least 8 hours before dose, mean C_{max} and $AUC_{0-\infty}$ ranged from approximately 53 to 134 ng/mL and 845 to 2157 ng·h⁻¹·mL⁻¹, respectively, after single doses of 30, 50, or 70-mg LDX; mean t_{max} and $t_{1/2}$ ranged from 3.41 to 3.58 hours and 8.61 to 8.90 hours, respectively.⁷

Parents of children with ADHD have reported that their children have difficulty or dislike taking their medication when it is administered as a tablet.⁸ Furthermore, it is reasonable to speculate that some adults with ADHD have difficulty taking their ADHD medication because a proportion of the adult population reports difficulty in swallowing medications.⁹ Therefore, having alternate methods to administer LDX could ease administration across individuals of any age group. LDX is currently approved to be administered as an intact capsule or the contents of the capsule may be consumed immediately after being emptied and completely dispersed in water, orange juice, or yogurt.² The primary objective of this study was to compare the pharmacokinetic profiles of LDX and D-amphetamine between 2 modes of oral administration in healthy, fasted adults: when the contents of a 70-mg LDX capsule were mixed with a soft food (yogurt) or orange juice and when an intact 70-mg LDX capsule was swallowed whole. This study served as the basis for the recommendation that LDX could be mixed with orange juice or yogurt when administered to any age group. These vehicles were chosen because they are generally appealing to individuals across age groups. A secondary objective was to assess the safety and tolerability of a single dose of LDX from a capsule mixed with yogurt or orange juice compared with those of LDX from an intact capsule.

MATERIALS AND METHODS

Study Design and Treatment

This open-label, randomized, 3-period crossover study (ClinicalTrials.gov: NCT01890785) was conducted by Clinical Pharmacology of Miami, Inc. (Miami, FL), from July 15, 2013, to August 22, 2013. The study consisted of a screening phase that ended at least 28 days before the first treatment dose; 3 single-dose, 5-day treatment periods separated by a 7-day washout between treatments; and a follow-up period. Healthy men or women (18–55 years old) were admitted to the clinical research center 1 day before the initiation of each treatment period (day –1) and remained at the center through completion of all day 5 assessments for the treatment period.

The treatments consisted of (1) administration of LDX after the contents of a 70-mg capsule were mixed with 4 ounces of orange juice; (2) administration of LDX after the contents of a 70-mg capsule were mixed with 4 ounces of yogurt; or (3) administration of an intact 70-mg LDX capsule with 240 mL of room temperature water. At the beginning of the first treatment period, participants were randomly assigned to receive each of 3 treatments in 1 of 6 treatment sequences in a 1:1:1:1:1:1 ratio. Participants were assigned a 4-digit randomization number immediately before dosing on day 1 of the first treatment period after the eligibility had been determined. The randomization schedule was produced and held by the clinical research organization PRA Health

Sciences (Raleigh, NC). For all treatments, participants were required to consume each treatment within a 3-minute period, to fast overnight (approximately 10 hours) before dosing and for another 4 hours after dosing, and to refrain from fluid intake for 4 hours before and 2 hours after dosing. Additionally, participants were not permitted to lie down for 4 hours after dosing. A follow-up phone call was made 7 ± 2 days after the final treatment to identify any ongoing or new adverse events (AEs) and concomitant medications taken since discharge.

The protocol was approved by the institutional review board (Aspire IRB, Santee, CA) before the study initiation, and the study was conducted in accordance with the International Conference on Harmonization and Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent before participating in the study.

Participants

Men and nonpregnant, nonlactating women aged 18–55 years old who were healthy (ie, with no evidence of active or chronic disease after a detailed review of medical and surgical histories and a complete physical examination) were eligible to participate. Additionally, participants were required to have a body mass index between 18.5 and 30 kg/m² at the screening visit and hemoglobin values ≥ 12 g/dL at screening and on day –1 of treatment period 1. Study participants also needed to be able to swallow a dose of the study drug according to the study conditions and to comply with study procedures.

Exclusion criteria included current or recurrent disease (eg, cardiovascular, renal, liver, gastrointestinal, malignancy, or other conditions) that could affect the pharmacokinetics or pharmacodynamics of the study drug or clinical and laboratory evaluations; current or relevant physical or psychiatric illness that may make the participant unable to comply with study requirements, or complete the study, or that presented undue risk to the participant; in the investigator's judgment, significant illness within 2 weeks of the first dose of the study drug or significant history of anxiety, tension, or agitation; and currently considered a suicide risk or demonstrating suicidal ideation or had a previous suicide attempt. Individuals with histories or the presence of structural abnormalities, syncope, cardiac conduction problems, exercise-related cardiac events, clinically relevant bradycardia, symptomatic cardiovascular disease, advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, transient ischemic attack, stroke, and vulnerability to sympathomimetic effects of stimulants were excluded, as were those with a family history of sudden cardiac death or ventricular arrhythmia, a history of controlled or uncontrolled hypertension, or with resting supine systolic blood pressure (SBP) >139 mm Hg or diastolic blood pressure (DBP) >89 mm Hg. Individuals were also excluded if they had known or suspected intolerance or hypersensitivity to the study drug, to closely related compounds, or to orange juice or vanilla yogurt; if they had used another investigational product within 30 days before receiving the first dose of the study drug; or if they had an inability to follow a standardized diet and meal schedule, or inability to fast. Individuals could not be enrolled if they used any medication that was known to

inhibit or induce the cytochrome P450 enzymes responsible for metabolism of the study drug within 14 days of the first dose of the study drug.

Study Endpoints

Pharmacokinetics

Based on the previous LDX pharmacokinetic assessments⁴ and the dose of LDX used in this study, blood samples for pharmacokinetic assessment were collected on treatment days 1 (30 minutes before dose and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours after dose), 2 (24 and 36 hours after dose), 3 (48 hours after dose), 4 (72 hours after dose), and 5 (96 hours after dose) during each treatment period.

Pharmacokinetic endpoints for LDX and D-amphetamine included t_{\max} , C_{\max} , $AUC_{0-\infty}$, $t_{1/2}$, area under the curve from the time of dosing to the last measurable concentration (AUC_{last}), first-order rate constant associated with the terminal (log-linear) portion of the curve (λ_z), total body clearance for extravascular administration divided by the fraction of the absorbed dose (CL/F), and the volume of distribution associated with the terminal slope after extravascular administration divided by the fraction of dose absorbed (Vz/F).

Bioanalytical Methodology

Plasma concentrations of LDX and D-amphetamine were measured using validated liquid chromatography–tandem mass spectrometry methods. For the analysis, 50 μL of internal standard was added to a 100- μL aliquot of plasma. Proteins were precipitated by the addition of 500 μL of a chilled acetonitrile/formic acid (100:5; volume:volume) solution. After vortex and centrifugation, the supernatant was removed, evaporated under nitrogen at 40°C, and reconstituted to a volume of 300 μL . A 10- μL sample was injected into the liquid chromatography–tandem mass spectrometry system and analyzed using an API 4000 mass spectrometer (AB SCIEX, Framingham, MA) coupled with a Shimadzu LC system (Shimadzu, Kyoto, Japan).

Plasma concentrations were calculated using an 8-point standard curve. The lower limit of quantification was 1 ng/mL for LDX and 2 ng/mL for D-amphetamine; calibration standards in human plasma ranged from 1 to 100 ng/mL for LDX and from 2 to 200 ng/mL for D-amphetamine (QPS, Newark, DE). Quality control samples for LDX (3, 20, and 80 ng/mL) and D-amphetamine (6, 40, and 160 ng/mL) were prepared in separate batches and stored at -20°C. In regard to assay performance, coefficients of variation and biases for LDX, respectively, were 7.0% and -5.0% at 3 ng/mL, 5.3% and -6.0% at 20 ng/mL, and 4.4 and -2.8 at 80 ng/mL. For D-amphetamine, coefficients of variation and biases, respectively, were 5.7% and -4.0% at 6 ng/mL, 2.4% and -5.3% at 40 ng/mL, and 2.1% and -2.5% at 160 ng/mL.

Safety and Tolerability

Safety assessments included recording of AEs, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations. AEs were recorded at screening, on all days during each treatment period, and at follow-up. Clinical laboratory evaluations and physical examinations were conducted at screening, day -1, and day

5 for each treatment period. Vital signs were assessed at screening, day -1, 30 minutes before dose and 0.5, 2, 4, 8, 12, 24, 48, 72, and 96 hours after dose during each treatment period. Twelve-lead ECGs were performed at screening, day -1, 30 minutes before dose, and 96 hours after dose of each treatment period.

Other Measurements

A 5-point Likert scale (1 = “bad” to 5 = “excellent”) was used to rate the overall taste of LDX in the orange juice or yogurt. Participants completed the questionnaire within 2 minutes of ingestion on day 1 of treatment.

Data Analysis

The sample size was estimated using nQuery 6.0 (Statistical Solutions, Boston, MA) for a 2 \times 2 crossover design and converted to a 3 \times 3 crossover, as previously described.¹⁰ To achieve 85% power (1-sided $\alpha = 0.05$; true mean ratio = 1.05), 24 participants (4 per sequence) were required to complete the study based on the estimate of the true within-subject SD for D-amphetamine of 0.215.⁴

Pharmacokinetic analyses were based on the pharmacokinetic analysis set (all participants in the safety analysis set for whom primary pharmacokinetic data were sufficient and interpretable). All statistical analyses were performed using SAS (SAS Institute, Cary, NC) Version 9.1.3 or higher. Descriptive statistics were calculated for all pharmacokinetic parameters. Log-transformed pharmacokinetic parameters for LDX and D-amphetamine among the 3 treatments were compared using analysis of variance for a crossover design with fixed factors for sequence, treatment, and period and random factors for subject within sequence.

Relative bioavailability of the 2 test treatments (LDX in orange juice and in yogurt) compared with the reference treatment (intact LDX capsule) was determined for D-amphetamine (the active moiety) and LDX (the pharmacologically inactive prodrug) using bioequivalence-testing procedures. Point estimates and 90% confidence interval [CI] for the comparisons of C_{\max} , $AUC_{0-\infty}$, and AUC_{last} (LDX in orange juice versus the intact LDX capsule; LDX in yogurt vs. the intact LDX capsule) were calculated. If the 90% CIs of the geometric mean ratios were within the interval of 0.8–1.25, equivalence was assumed. If the 90% CIs were not fully contained within the 0.8 to 1.25 interval, a difference between the test and reference treatments could not be excluded, and the mean ratio estimates and their CIs were assessed. Safety endpoints were summarized using descriptive statistics from the safety analysis set (participants taking ≥ 1 study drug dose and having ≥ 1 postdose safety assessment).

RESULTS

Participant Disposition and Demographics

Thirty participants were enrolled in the study; all participants were included in the randomized, pharmacokinetic, and safety analysis sets (see **Figure, Supplemental Digital Content 1**, <http://links.lww.com/TDM/A166>). One participant

requested to be withdrawn the day after receiving LDX mixed with orange juice during treatment period 3; no AEs were reported for this participant. Participant demographics are summarized in Table 1.

Pharmacokinetics

Linear scale plots for mean ± SD plasma concentrations over time by treatment for LDX and D-amphetamine are shown in Figures 1A, B. Across treatments, LDX concentrations reached a maximum at 1 hour after dose and returned to predose levels after 4 hours. Mean peak LDX plasma concentrations were generally comparable across treatments but tended to be higher after administration of the intact capsule compared with LDX mixed with orange juice or yogurt. Plasma concentration versus time profiles for D-amphetamine were similar; mean peak plasma concentrations were observed at 4 hours after dose for all treatments and returned to pretreatment levels after 72 hours.

Descriptive statistics for all pharmacokinetic parameters are summarized in Table 2. Mean values for LDX C_{max} and AUC_{last} were the lowest after LDX was mixed with orange juice and the highest after administration of the intact LDX capsule. Mean values for LDX AUC_{0-∞} were lowest after LDX was mixed with orange juice and similar when LDX was mixed with yogurt or administered as an intact capsule. Mean t_{1/2} and t_{max} values for LDX were similar across all 3 treatments; the mean LDX CL/F value was higher after LDX was mixed with orange juice compared with being mixed with yogurt or administered as an intact capsule. For D-amphetamine, mean values for C_{max}, AUC_{last}, CL/F, t_{1/2}, and t_{max} were similar across all of the treatments. The mean AUC_{0-∞} value for D-amphetamine was slightly lower when LDX was mixed with yogurt compared with being mixed with orange juice or administered as an intact capsule.

TABLE 1. Baseline Demographic Characteristics, Safety Analysis Set

	Total Participants (N = 30)
Age, yr	
Mean ± SD	37.6 ± 10.07
Range	18–53
Sex, n (%)	
Male	22 (73.3)
Female	8 (26.7)
Race, n (%)	
White	27 (90)
Black or African American	3 (10)
Ethnicity, n (%)	
Hispanic or Latino	18 (60.0)
Not Hispanic or Latino	12 (40.0)
Mean ± SD weight, kg	77.31 ± 12.093
Mean ± SD height, cm	169.8 ± 9.46
Body mass index, kg/m ²	26.760 ± 2.9427

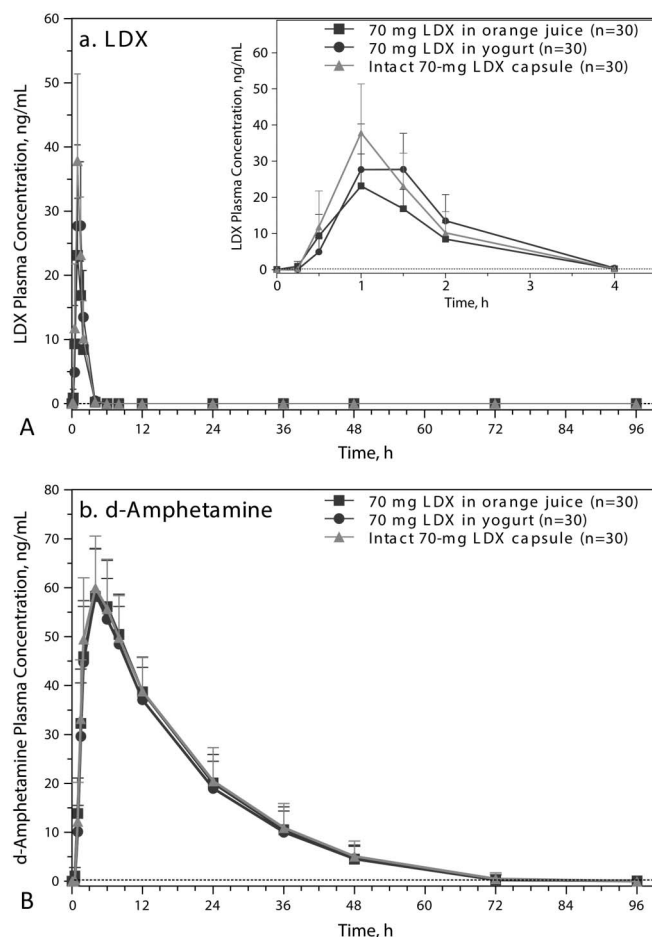


FIGURE 1. Plasma concentration versus time plots for (A) LDX and (B) D-Amphetamine by treatment regimen, pharmacokinetic analysis set.

Geometric least squares mean (LSM) and the ratios of the geometric LSM for C_{max}, AUC_{0-∞}, and AUC_{last} are summarized in Table 3. For LDX (the inactive prodrug), geometric LSM ratios and their respective 90% CIs for C_{max}, AUC_{0-∞}, and AUC_{last} fell entirely below the lower limit of the prespecified range when mixed with orange juice compared with the intact LDX capsule. Geometric LSM ratios and the respective 90% CIs for LDX AUC_{0-∞} and AUC_{last} fell within the prespecified range when mixed with yogurt compared with the intact LDX capsule; the lower 90% CI for LDX C_{max} fell below the lower limit of the prespecified range. For D-amphetamine (the active moiety), the geometric LSM ratios and their 90% CIs for C_{max}, AUC_{0-∞}, and AUC_{last} all fell entirely within the prespecified range when LDX was mixed with orange juice or yogurt compared with administration as an intact capsule.

The observed total variability for D-amphetamine for all 3 treatment groups in the pharmacokinetic analysis set was 24.6% (95% CI, 19.5%–33.4%) for log-transformed AUC_{0-∞} and 17.3% (95% CI, 13.7%, 23.2%) for log-transformed C_{max}. Intrasubject variability (95% CI) for log-transformed AUC_{0-∞} and C_{max} was 7.6% (6.4%, 9.3%) and 6.3%

TABLE 2. Pharmacokinetic Parameters (Mean ± SD) by Treatment, Pharmacokinetic Analysis Set

	C_{max} , ng/mL	t_{max} , h	AUC_{last} , ng·h ⁻¹ ·mL ⁻¹	$AUC_{0-∞}$, ng·h ⁻¹ ·mL ⁻¹
LDX				
Orange juice	24.5 ± 7.48*	1.1 ± 0.2*	27 ± 7.8*	33.3 ± 9.7†
Yogurt	32.2 ± 11.46*	1.3 ± 0.3*	36 ± 14.2*	46.4 ± 15.4‡
Intact capsule	38.54 ± 13.07*	1.1 ± 0.2*	38.3 ± 12.3*	43.8 ± 15§
D-Amphetamine				
Orange juice*	59.11 ± 9.47	4.8 ± 1.1	1140.9 ± 274.1	1230.9 ± 291.7
Yogurt*	59.02 ± 9.28	4.2 ± 0.6	1110.1 ± 252.9	1180.4 ± 275.6
Intact capsule*	61.01 ± 10.81	3.8 ± 1.1	1180.2 ± 295.1	1252.4 ± 315.3
	λ_z , h ⁻¹	$t_{1/2}$, h	CL/F, L/h	Vz/F, L
LDX				
Orange juice	1.3852 ± 0.3974†	0.54 ± 0.16†	2334.63 ± 894†	1781.62 ± 740.08†
Yogurt	1.2748 ± 0.2399‡	0.57 ± 0.15‡	1650.07 ± 472.24‡	1385.27 ± 702.55‡
Intact capsule	1.4982 ± 0.4608§	0.52 ± 0.22§	1770.23 ± 568.51§	1289.81 ± 564.82§
D-Amphetamine				
Orange juice*	0.0622 ± 0.013	11.61 ± 2.41	59.86 ± 13.86	969.91 ± 166.91
Yogurt*	0.0613 ± 0.0124	11.72 ± 2.2	62.65 ± 15.86	1026.5 ± 182.1
Intact capsule*	0.0621 ± 0.0124	11.57 ± 2.15	59.26 ± 14.52	960.07 ± 174.42

*n = 30.
†n = 22.
‡n = 17.
§n = 24.

$AUC_{0-∞}$, area under the plasma concentration versus time curve extrapolated to infinity (calculated using the observed value of the last nonzero concentration); AUC_{last} , area under the plasma concentration versus time curve to last assessment; CL/F, total body clearance for extravascular administration divided by the fraction of dose absorbed; C_{max} , maximum plasma concentration; LDX, lisdexamfetamine; $t_{1/2}$, terminal half-life; t_{max} , time of maximum observed concentration; Vz/F, volume of distribution associated with the terminal slope after extravascular administration divided by the fraction of dose absorbed; λ_z , first-order rate constant associated with the terminal (log-linear) portion of the curve.

(5.4%, 7.8%), respectively. Intersubject variability (95% CI) for log-transformed $AUC_{0-∞}$ and C_{max} was 23.4% (18.2%, 33.0%) and 16.1% (12.4%, 22.8%), respectively.

Safety and Tolerability

Across all treatment regimens, 73.3% of participants (22/30) reported a treatment-emergent AE (TEAE); the frequency of TEAEs by treatment is summarized in Table 4. Only 1 TEAE was not considered to be related to the study drug. There were no serious or severe TEAEs; no TEAEs led

to study discontinuation. All TEAEs were categorized as mild in severity. TEAEs reported in ≥1 participant in any treatment regimen are summarized in Table 4. The TEAEs reported most frequently across all treatments were decreased appetite, dry mouth, and headache.

There were no apparent differences between treatment groups for changes in pulse, DBP, or SBP (Table 5). Mean pulse increased to maximum levels at 12 hours after treatment and returned to pretreatment levels by 48 hours after dose. Mean SBP increased to maximum levels at 4 hours after

TABLE 3. Geometric Means for C_{max} , $AUC_{0-∞}$, and AUC_{last} by Treatment, Pharmacokinetic Analysis Set

	C_{max} , ng/mL (N = 30)		$AUC_{0-∞}$, n·h ⁻¹ ·mL ⁻¹ (N = 30)		AUC_{last} , ng·h ⁻¹ ·mL ⁻¹ (N = 30)	
	Geometric LSM	Ratio (90% CI) of Geometric LSM*	Geometric LSM	Ratio (90% CI) of Geometric LSM*	Geometric LSM	Ratio (90% CI) of Geometric LSM*
LDX						
Orange juice	23.46	0.641 (0.582, 0.707)	30.33	0.716 (0.647, 0.792)	25.88	0.708 (0.655, 0.766)
Yogurt	30.30	0.828 (0.752, 0.912)	42.38	1.000 (0.896, 1.116)	33.54	0.918 (0.849, 0.992)
Intact capsule	36.59	NA	42.39	NA	36.55	NA
D-Amphetamine						
Orange juice	58.33	0.971 (0.945, 0.998)	1200	0.986 (0.955, 1.019)	1112	0.970 (0.937, 1.004)
Yogurt	58.26	0.970 (0.944, 0.997)	1149	0.945 (0.915, 0.976)	1083	0.944 (0.912, 0.977)
Intact capsule	60.06	NA	1216	NA	1147	NA

*Reference treatment is the intact LDX capsule.

$AUC_{0-∞}$, area under the plasma concentration versus time curve extrapolated to infinity; AUC_{last} , area under the plasma concentration versus time curve to last assessment; C_{max} , maximum plasma concentration; LDX, lisdexamfetamine; LSM, least squares mean; NA, not applicable.

TABLE 4. Summary of TEAEs,* Safety Analysis Set

	Orange Juice (N = 30)		Yogurt (N = 30)		Intact Capsule (N = 30)	
	n (%)	No. Events	n (%)	No. Events	n (%)	No. Events
Any TEAE	16 (53.3)	20	17 (56.7)	20	10 (33.3)	15
Any serious TEAE	0 (0)	0	0 (0)	0	0 (0)	0
TEAE-related to study drug	16 (53.3)	19	17 (56.7)	20	9 (30.0)	14
TEAE leading to study discontinuation	0 (0)	0	0 (0)	0	0 (0)	0
Any severe TEAE	0 (0)	0	0 (0)	0	0 (0)	0
TEAE reported by ≥1 participant in any treatment group						
Decreased appetite	9 (30.0)	9	8 (26.7)	8	3 (10.0)	3
Dry mouth	3 (10.0)	3	5 (16.7)	5	3 (10.0)	3
Headache	4 (13.3)	4	3 (10.0)	3	4 (13.3)	4
Dizziness	1 (3.3)	1	2 (6.7)	2	1 (3.3)	1
Psychomotor hyperactivity	1 (3.3)	1	2 (6.7)	2	1 (3.3)	1
Anxiety	0 (0)	0	0 (0)	0	2 (6.7)	2
Carbuncle	0 (0)	0	0 (0)	0	1 (3.3)	1
Back pain	1 (3.3)	1	0 (0)	0	0 (0)	0
Agitation	1 (3.3)	1	0 (0)	0	0 (0)	0

*Participants were counted by the treatment most recently taken when the event occurred and were counted once per category per treatment. TEAE, treatment-emergent adverse event.

treatment and returned to pretreatment levels by 48 hours after dose. Mean DBP increased to maximum levels at 2 hours after treatment and returned to pretreatment levels by 48 hours after dose. Mean changes from baseline in ECG heart rates and interval were small, with no apparent differences between treatments (data not shown).

TABLE 5. Mean ± SD Change From Baseline in Pulse Rate, SBP, and DBP, Safety Analysis Set

	Orange Juice (N = 30)	Yogurt (N = 30)	Intact Capsule (N = 30)
Pulse rate, bpm			
2 h	4.6 ± 11.83	2.8 ± 13.09	1.0 ± 13.30
4 h	6.3 ± 11.95	5.2 ± 14.55	4.3 ± 14.12
12 h	13.4 ± 11.94	13.3 ± 10.35	14.2 ± 12.75
24 h	5.8 ± 12.12	6.2 ± 12.72	6.4 ± 11.89
48 h	0.3 ± 11.73	-0.4 ± 10.77	0.1 ± 12.06
SBP, mm Hg			
2 h	19.2 ± 12.29	15.7 ± 12.84	20.9 ± 11.81
4 h	21.4 ± 9.30	20.8 ± 10.23	20.4 ± 10.71
12 h	9.6 ± 10.48	12.5 ± 9.37	10.4 ± 7.80
24 h	3.4 ± 10.27	4.7 ± 8.55	3.2 ± 9.79
48 h	-1.7 ± 8.72	-1.1 ± 10.01	-1.0 ± 8.25
DBP, mm Hg			
2 h	11.0 ± 10.08	10.8 ± 11.41	10.2 ± 9.58
4 h	10.8 ± 8.44	9.6 ± 9.93	8.6 ± 13.05
12 h	4.9 ± 7.13	5.3 ± 6.76	5.4 ± 6.27
24 h	3.4 ± 8.37	2.2 ± 7.23	4.0 ± 8.07
48 h	1.2 ± 7.15	0.9 ± 6.33	0.9 ± 6.88

bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Ratings of Taste

Most participants rated the taste of LDX when mixed with orange juice [good, 15/30 (50.0%); excellent, 9/30 (30.0%)] or yogurt [good, 10/30 (33.3%); excellent, 16/30 (53.3%)] as good or excellent.

DISCUSSION

The purpose of this study was to compare the relative bioavailability of LDX and D-amphetamine when LDX from a capsule is mixed with soft food or liquid, such as yogurt or orange juice, versus when LDX is administered as an intact capsule. The main findings demonstrate that the relative bioavailability of the active moiety, D-amphetamine, based on C_{max} and AUC, is not different from that of an intact LDX capsule when LDX is mixed with orange juice or yogurt. The pharmacokinetic profile of D-amphetamine, including t_{max} and $t_{1/2}$, observed when LDX was mixed with yogurt or orange juice in this study was comparable to previous reports in single-dose studies of healthy adults.³⁻⁵ Intrasubject variability for D-amphetamine was low and within one third to one half of the corresponding intersubject variability. These findings indicated that LDX was suitable for use in adults when swallowed as an intact capsule, when mixed with a soft food such as yogurt, or when mixed with a liquid such as orange juice. Although these data supported a subsequent label change for LDX in the United States,² this is the first detailed description of these findings.

The ability to mix the contents of LDX capsules in soft food or liquids for the purpose of administration is consistent with reports for other ADHD medications.¹¹⁻¹⁴ Metadate CD (extended-release methylphenidate HCl capsules; UCB, Inc.,

Smyrna, GA),¹² Adderall XR (extended-release mixed amphetamine salts; Shire US Inc., Wayne, PA),¹³ and Focalin XR (extended-release dexamethylphenidate hydrochloride; Novartis Pharmaceuticals Corp., East Hanover, NJ)¹⁴ are approved to be swallowed whole or sprinkled on applesauce and consumed immediately. Using standard bioequivalence-testing procedures, studies of Adderall XR¹⁵ and Metadate CD¹⁶ reported comparable relative bioavailability of the active ingredients under fasting conditions in healthy adults when the contents of a capsule were sprinkled over a small amount of applesauce compared with the intact capsule swallowed whole.

In contrast to the findings for D-amphetamine, relative bioavailability of LDX when mixed with orange juice or yogurt was lower compared with that from an intact LDX capsule, with geometric LSM ratios and 90% CIs for C_{\max} , $AUC_{0-\infty}$, and AUC_{last} falling below the prespecified bioequivalence range when LDX was mixed with orange juice and the lower CI for C_{\max} falling below the lower limit of the prespecified bioequivalence range when LDX was mixed with yogurt. The reason for this discrepancy between the bioavailabilities of D-amphetamine and LDX is not known. However, as D-amphetamine is pharmacologically active whereas LDX is not¹ and the reduced bioavailability of LDX when mixed with orange juice or yogurt does not result in reduced D-amphetamine bioavailability, the observed changes in overall LDX concentrations may not have clinical significance.

The safety and tolerability profile of LDX did not substantially differ across treatments, and no unexpected TEAEs or vital sign changes were observed. There were no serious or severe TEAEs; all TEAEs were considered mild in severity. Among the most frequently reported TEAEs (decreased appetite, dry mouth, and headache), dry mouth and headache have been previously reported in healthy adults administered LDX³⁻⁵; decreased appetite, dry mouth, and headache have also been reported in clinical studies of LDX in children, adolescents, and adults with ADHD.¹⁷⁻¹⁹ The patterns of changes in pulse and blood pressure are also consistent with previously published findings in healthy adults.^{3,4}

These data should be considered in light of several potential limitations. First, findings related to safety and tolerability from this phase 1 study should be interpreted with caution because the sample size was small and participants were predominantly male. Second, data related to the taste acceptability of LDX mixed with orange juice or yogurt were exploratory in nature. Third, because this is a single-dose study, it is not known whether differences in bioavailability would be observed if lower doses of LDX were administered or if LDX was mixed with different foods or liquids.

CONCLUSIONS

This was the first study to compare the relative bioavailability of LDX when the contents of a capsule were mixed with soft food or liquids with that of an intact LDX capsule when swallowed whole in healthy adults. The relative bioavailability of D-amphetamine did not differ when LDX was mixed with orange juice or yogurt compared with LDX being taken as an intact capsule. These results support the administration of LDX in orange juice or soft foods such as yogurt as

an appropriate alternative to swallowing intact capsules. Most of the participants rated the taste of LDX in orange juice or yogurt as acceptable, good, or excellent. This suggests that the administration of LDX in these vehicles may not negatively affect LDX use in individuals who require an alternative mode of administration to swallowing an intact LDX capsule.

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