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ORIGINAL ARTICLE

Multiple daily-dose pharmacokinetics of lisdexamfetamine dimesylate in healthy adult volunteers

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ABSTRACT

Objective: To evaluate the pharmacokinetics of lisdexamfetamine dimesylate (LDX; Vyvanse*) in fasting healthy adult volunteers.

Background: LDX is the first pro-drug stimulant and is indicated for the treatment of attention-deficit/hyperactivity disorder. LDX was developed with the goal of providing an extended effect that is consistent throughout the day, with a reduced potential for abuse, overdose toxicity, and drug tampering.

Methods: This was an open-label, multiple-dose phase 1 study. LDX 70 mg/d was administered in the morning to 12 subjects for 7 days. Twenty blood samples were drawn during the study. Descriptive statistics were used for pharmacokinetic parameters.

Results: Based on C_{min}, steady-state d-amphetamine concentration (20.6 ng/mL) was reached by day 5, whereas LDX was undetectable, and 95% of the d-amphetamine was eliminated within 48 hours following the final dose on day 7. At steady state, d-amphetamine achieved a mean ± standard deviation C_{max} of 90.1 ± 29.6 ng/mL, with a median T_{max} of 3.0 hours. The AUC_{0-inf} for d-amphetamine was 1453 ± 645.7 ng·h/mL. Complete elimination of the pro-drug occurred approximately 6 hours following the final dose on day 7. Adverse events were mild to moderate and similar to other oral amphetamines.

Conclusions: This study describes the steady-state pharmacokinetics of LDX, a new pro-drug stimulant. Possible study limitations include an open-label design and a small sample size.

Introduction

The prevalence of attention-deficit/hyperactivity disorder (ADHD) is estimated to be 8% to 10% in school-aged children and approximately 4% in the adult population[1–3]. Psychostimulant medications, specifically amphetamines and methylphenidate, have the strongest evidence for efficacy and safety and are considered first-choice treatments in the management of ADHD[4].

Despite many years of clinical experience and demonstrated efficacy of stimulant therapies in children with ADHD, concerns remain regarding the potential for toxicity, diversion, overdose, and abuse[5,6]. The abuse potential of a stimulant medication is partly dependent on its pharmacokinetic profile. Increased abuse liability has been related to the time to reach maximum concentration[7]. Immediate-release stimulants produce high concentration spikes in a relatively short time, rapidly maximizing dopamine transporter occupancy

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and, therefore, have greater potential for abuse than agents that gradually increase drug concentrations in the blood[8]. The development of extended-release formulations of stimulants has sought to address this problem while having a profile that supports therapeutic activity soon after administration[7].

Lisdexamfetamine dimesylate (LDX; Vyvanse*) is the first pro-drug stimulant and is indicated for the treatment of ADHD. LDX is a therapeutically inactive molecule. After oral ingestion, LDX is converted to l-lysine, a naturally occurring essential amino acid, and active d-amphetamine, which is responsible for the drug's activity. LDX was developed with the goal of providing an extended duration of effect that is consistent throughout the day, with a reduced potential for abuse, overdose toxicity, and drug tampering. When LDX is administered orally, the pharmacokinetic profile of d-amphetamine is comparable to extended-release formulations of available stimulants. For example, following a 7-day treatment course of mixed amphetamine salts extended release (MAS XR; Adderall XR†) 30 mg once daily, the peak plasma concentration of d-amphetamine of 67 ng/mL was attained in 4 hours[9]. When administered parenterally, a route employed for abuse, animal studies have shown that only small amounts of d-amphetamine are released from LDX[10].

LDX has been shown to be effective in improving ADHD symptoms in children, with a side effect profile comparable to other stimulant medications[11–13]. LDX improved symptoms of ADHD as early as the first week of treatment, and extending up to 1 year, with significant improvement in symptoms lasting into the evening after early morning dosing. To determine whether LDX is also effective in adults with ADHD, it was first necessary to conduct pharmacokinetic studies, preparatory to establishing dose and frequency. This phase 1 open-label, multiple-dose study assessed the steady-state pharmacokinetics, tolerability, and safety of oral LDX 70 mg in healthy adult volunteers following a 7-day, once-daily treatment course.

Methods

Subjects

Healthy men and women between the ages of 18 and 55 years were eligible to volunteer in this open-label, multiple-dose, single-center phase 1 study. All subjects were given a physical examination, and their medical and medication histories were noted. Participants were included if they had a body weight that ranged from ± 15% of the ideal for height and frame size according to the Metropolitan Life Insurance Company Statistical Bureau Tables. Pregnant women and subjects using prescription or nonprescription medications were excluded from the trial, as were subjects with any clinically significant and/or chronic condition that would, in the opinion of the investigator, jeopardize or otherwise compromise the safety of the participant or the validity of the study results. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonisation Guidelines. The clinical study protocol and the written informed consent forms were approved by the local Institutional Review Board (IRB). The study was conducted by CEDRA Corporation, Austin, Texas, and the local IRB used was Integreview (www.integreview.com).

Study design

After undergoing a pre-study screening, participants were administered LDX 70 mg capsules with 8 ounces of room temperature water once daily (7:00 AM) for 7 consecutive days. Study medication was administered in the clinic to ensure adherence, and participants were confined overnight on day 6 to ensure fasting prior to sample collection on day 7. The once-daily 70 mg LDX dose was selected since it was the highest dose under evaluation in clinical safety and efficacy trials and contains d-amphetamine approximately equivalent to MAS XR at 30 mg. The dose for the study was discussed with and approved by the US Food and Drug Administration (FDA) for the study design.

Subjects returned to the research center as instructed on the morning of day 1. After interviewing the subject, the study coordinator filled out a brief questionnaire to confirm that the inclusion/exclusion criteria had not been violated since the screening. A urine sample was collected for drug screening, as well as for pregnancy testing of all female subjects. Any new concomitant medications (CMEDs) or adverse events (AEs) were recorded and evaluated by a study investigator prior to dosing. Sitting vital signs (respiratory rate, heart rate, blood pressure, and oral temperature) were taken after 5 minutes of rest, and repeat heart rate and blood pressure were assessed after a 2-minute stand. A pre-dose blood draw was taken, subjects were assigned a subject number, and drug was administered.

Subjects returned to the research center each morning at the designated time on days 2 through 6 for safety evaluation and dose administration. Pre-dose vital signs (sitting heart rate and blood pressure after 5 minutes of

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† Adderall XR is a registered trade name of Shire US Inc, Wayne, PA, USA

rest), repeat vital signs after a 2-minute stand, and AEs and CMEDs were recorded and evaluated to ensure that subjects should continue to receive the drug. A pre-dose blood draw was taken (days 5 and 6 only) and drug was dosed at approximately 7:00 AM.

Subjects were admitted to the research center (confinement facility) in the evening approximately 12 hours prior to the scheduled day 7 dose the next morning. They remained in the clinic until completion of the 24-hour post day 7 dose blood collection and procedures. AEs and CMEDs were recorded and evaluated to ensure that the subject should continue to dose; blood was collected for plasma quantitation of d-amphetamine and intact LDX at 0 (dose time), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours post day 7 dose. Sitting vital signs (heart rate and blood pressure) were measured after 5 minutes of rest at 0 (dose time), and 1, 2, 4, 8, and 12 hours post day 7 dose. Repeat vital signs were taken after a 2-minute stand, and subjects were dosed at approximately 7:00 AM. Standardized meals were allowed at 4 and 9 hours post-dose with a snack at 13 to 14 hours post-dose.

On days 8, 9, and 10 (study exit), AEs and CMEDs were recorded and evaluated, sitting vital signs (heart rate and blood pressure) were taken after 5 minutes of rest, approximately 48 and 72 hours post day 7 dose, respectively, and repeat vital signs were measured after a 2-minute stand. Blood was collected for plasma quantitation of d-amphetamine and intact LDX at 24, 48, and 72 hours post day 7 dose. Subjects were instructed on study restrictions before being discharged from the center and the details about their next visit or exit from the study on day 10. Similar procedures were followed if a subject was terminated early.

Thirty days after the last dose, subjects were followed up with a telephone call to assess the status of unresolved non-serious AEs or serious AEs and whether any new serious AEs had occurred since study completion or early termination.

Blood sample collection and bioanalytical methods

Venous blood samples (7 mL) were drawn into EDTA Vacutainer tubes before medication dosing on the morning of days 1, 5, 6, and 7, and at 16 additional time points (hours 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, and 72) after final dosing on day 7. Subjects fasted for at least 10 hours before and 4 hours after final dosing on day 7. Twenty blood samples were collected during the study as specified above. Approximately 140 mL of blood were collected from each subject for analysis of d-amphetamine and LDX levels. Immediately after each collection, the Vacutainer tube was centrifuged at 4°C, 3000 rpm, for 10 minutes. Within approximately 60 minutes of collection, samples were stored in a polypropylene container labeled with the protocol number, day number, subject randomization number, collection date, and time point. All plasma samples were stored at approximately –20°C or below.

Plasma samples were assayed by the CEDRA Corporation, using a method consisting of liquid chromatography with tandem/mass spectrometry; this method was validated for concentrations of d-amphetamine ranging from 2.00 to 200 ng/mL and for concentrations of intact LDX ranging from 1.00 to 100 mg/mL. The combined internal standard was a solution of amphetamine-D_5 and LDX. From the plasma drug levels, pharmacokinetic parameters for both d-amphetamine and intact LDX were calculated using non-compartmental methods. Human plasma samples containing amphetamine, LDX, and the appropriate internal standards were extracted with an organic solvent mixture and analyzed on a SCIEX API 3000 LC-MS-MS equipped with an HPLC column. The peak area of the m/z 136→91 amphetamine product ion was measured against the peak area of the m/z 141→96 amphetamine-D_5 internal standard product ion. The peak area of the m/z 264→84 LDX product ion was measured against the peak area of the m/z 272→92 LDX-D_8 internal standard product ion. Quantitation was performed using separate weighted ($1/x^2$) linear least squares regression analyses generated from fortified plasma calibration standards prepared immediately prior to each run. The observed within-run and between-run coefficients of variation (CV%) at the lower limit of quantification (LLOQ) were 2.3% and 14.7%, respectively, for d-amphetamine and 1.2% and 9.9%, respectively, for LDX.

Quality control (QC) pools were prepared by fortifying human plasma with a combined intermediate solution (i.e., standard working solution) at the appropriate concentrations. The QC pools were qualified while fresh and stored at approximately –20°C or below. High, medium, and low QC samples were prepared at 160, 40, and 6 ng/mL for amphetamine and 80, 20, and 3 ng/mL for LDX. To qualify a new QC pool, six QCs were analyzed at each concentration level. The precision of the back-calculated values had to be ≤ 15% for each pool level, and the accuracy could not deviate more than ± 15% from the theoretical concentration for each pool level. If available, a previously qualified set of QCs were analyzed in the same run to qualify the batch.

At least two QC samples from each concentration were extracted with the study samples. At least two-thirds of all QC samples and at least half at each concentration level had to be within 15% of their theoretical concentration for a sample analysis run to meet acceptance for QC samples; other criteria applied.

Pharmacokinetic analysis

Pharmacokinetic parameters were computed for d-amphetamine and intact LDX using non-compartmental methods with WinNonlin (Enterprise Version 4.0, Pharsight Corporation, Cary, North Carolina, USA). AUC_{0-t} is defined as area under the drug concentration-time curve from time 0 to time '*t*,' where '*t*' is the last time point with a drug concentration equal to or greater than the validated lower limit of the assay (C_t). AUC_{0-24} is area under the drug concentration-time curve from time 0 to 24 hours. The average concentration (C_{avg}) is the AUC_{0-24} divided by 24. $C_{max,ss}$ was defined as maximum observed drug concentration at steady state over the time interval of 0 to 24 hours on day 7. $C_{min,ss}$ was defined as minimum observed drug concentration at steady state over the time interval of 0 to 24 hours on day 7. $T_{max,ss}$ is the time at which $C_{max,ss}$ was reached. Fluctuation Index (FI) was defined as the difference between C_{max} and C_{min} divided by C_{avg}. Analyses of pharmacokinetic parameters were performed separately for d-amphetamine and intact LDX in the protocol-defined pharmacokinetic population. Drug plasma concentration-time plots were produced for individual subjects by treatment.

Safety analysis

Safety parameters included AEs, clinical laboratory tests (chemistry, hematology, and urinalysis), medical history, physical examinations, 12-lead electrocardiogram (ECG), and vital signs. AEs were recorded from time of informed consent until study completion. Serious AEs were documented for up to 30 days after final dosing of study medication. The investigator assessed the severity of AEs and their relationship to the study medication. A comprehensive physical examination, including vital signs, ECG, and laboratory tests, was performed at pre-study screening and at final discharge.

Statistical methods

The pharmacokinetic population was defined as all participants who were treated with LDX and who gave blood samples for steady-state pharmacokinetic determination. Data from all participants in the pharmacokinetic group were evaluated for d-amphetamine and intact LDX. Descriptive statistics were number of subjects (*n*), mean, standard deviation (SD), and median, minimum, and maximum values, and were calculated for all pharmacokinetic parameters.

The point at which steady state was reached was determined by regression of pre-dose d-amphetamine concentrations over time on days 5, 6, and 7. Mean drug plasma concentration-time plots were produced by LDX with and without the standard error as the error bar. Descriptive summaries of pharmacokinetic parameters were presented by treatment, using number of observations, mean and SD, and CV%. The descriptive summaries of pharmacokinetic parameters were also reported for men and women, separately, with and without dose being normalized to patient weight. Steady state for the study medication was assessed using a simple regression analysis with the pre-dose concentrations of days 5, 6, and 7 as the dependent variable and the corresponding blood drawing day as the predictor. The standardized estimate of the slope with 95% confidence interval (CI) was reported. Steady state was concluded if the estimate of the slope was not statistically different from zero (i.e., $p > 0.05$).

Observed AEs were coded by MedDRA version 7.1 (Reston, Virginia, USA) preferred terminology. Treatment-emergent AEs (TEAEs) were reported by the preferred terminology and body system for incidence rate. Changes in vital signs from pre-dose were analyzed comparatively for each post-dose time point on day 7, using paired *t*-test. ECG parameters and laboratory tests were summarized descriptively.

Results

Subjects

Baseline characteristics of the 12 participants enrolled in the study are listed in Table 1. Eleven subjects

Table 1. *Demographic characteristics of the safety population (*n = *12)*

Characteristic	*n* (%) or reported values
Ethnicity/race	
White	6 (50)
Hispanic	6 (50)
Gender	
Male	4 (33)
Female	8 (67)
Height, cm	
Mean ± SD	167.1 ± 9.8
Median	162.8
Range	156.0–183.5
Weight, kg	
Mean ± SD	69.5 ± 10.7
Median	66.8
Range	55.1–84.4
Age, years	
Mean ± SD	37.0 ± 8.9
Median	40.0
Range	20.0–46.0

SD = standard deviation

received all seven doses of the study medication and were included in the pharmacokinetic population. The safety group included those 11 subjects, as well as one female subject who withdrew from the study after receiving only one dose. Data are not available for this patient as she was lost to follow-up. No CMEDs were used by any subject for the duration of the study.

Pharmacokinetics

Plasma d-amphetamine and LDX trough concentrations obtained at pre-dose, including day 1 (baseline) and day 8 (i.e., 24 hours post day 7 dose) are presented in Table 2. Based on comparison of pre-dose concentration values across study days, steady-state d-amphetamine concentrations were reached by day 5; concentrations on days 5, 6, and 7 were not significantly different. On day 5, the mean pre-dose concentration of d-amphetamine was 20.6 ng/mL, whereas LDX was undetectable. No quantifiable trough concentrations were noted at day 5 to day 7 for intact LDX, as would be expected, indicating that there was no drug accumulation for intact LDX and that it is rapidly eliminated following the administration of multiple daily doses of 70 mg.

Table 2. *Daily pre-dose (trough) plasma concentrations of d-amphetamine and intact LDX (*n = *11)*

Pre-dose day	d-amphetamine, ng/mL Mean (SD) [CV%]	Intact LDX, ng/mL Mean (SD) [CV%]
Day 1	0.0 (0.0) [–]	0.0 (0.0) [–]
Day 5	20.6 (11.8) [57.2]	0.0 (0.0) [–]
Day 6	18.7 (10.7) [57.0]	0.0 (0.0) [–]
Day 7	21.9 (17.2) [78.5]	0.0 (0.0) [–]
Day 8*	18.2 (10.7) [59.0]	0.0 (0.0) [–]

*Day 8 = 24 hours post day 7 dose

CV% = coefficient of variation; LDX = lisdexamfetamine dimesylate; SD = standard deviation

Pharmacokinetic values for d-amphetamine and intact LDX, following the day 7 dose of oral LDX 70 mg after fasting, are shown in Table 3. At steady state, the mean ± standard deviation C_{max} of d-amphetamine and LDX after a 70 mg LDX capsule were 90.1 ± 29.6 ng/mL and 47.9 ± 18.6 ng/mL, occurring at a median T_{max} of 3.0 hours and 1.0 hours, respectively. During a 24-hour dosing interval at steady state, the average d-amphetamine concentration (C_{avg}) was 46.4 ± 16.5 ng/mL, with a 164% fluctuation between the maximum and minimum concentrations relative to C_{avg}. The C_{avg} of LDX was 2.5 ± 0.9 ng/mL with an FI of 1900%. AUC is proportional to the fraction of drug absorbed only if clearance and dose are constant. In this case, when $AUC_{0–24}$ values are compared, the amount of active d-amphetamine is approximately 18 times greater than the amount of intact LDX. Maximum concentrations of both pro-drug and d-amphetamine are reached quickly, by 1.1 hours and 3.7 hours, respectively; in addition, the estimate of slope, calculated from the regression analysis of the pre-dose d-amphetamine concentrations on days 5, 6, and 7, was 0.654 (95% CI, –5.16, 6.47; $p > 0.82$), indicating that steady-state trough concentrations of d-amphetamine (C_{min}) were achieved by day 5.

Post-study plasma levels

Mean plasma levels of d-amphetamine and intact LDX following administration of oral LDX 70 mg on day 7 are illustrated in Figure 1. Plasma concentrations of d-amphetamine approached 0 at 72 hours following the final dose ($T_{½}$ = 10.1 hours). Intact LDX levels descended to 0 at 5 hours following the final dose ($T_{½}$ = 0.4 hours), and serum concentrations of d-amphetamine began to decline at the same time point following log-linear kinetics. Thus, intact LDX

Table 3. *Steady-state pharmacokinetic parameters for d-amphetamine and LDX following the administration of oral once-daily LDX 70 mg (*n = *11)*

	$C_{max,ss}$, ng/mL	T_{max}, h*	$AUC_{0–24}$, ng·h/mL	C_{avg}, ng/mL	$C_{min,ss}$, ng/mL	FI, %
d-amphetamine						
Mean (SD)	90.1 (29.6)	3.0 (1.4)	1110 (397)	46.4 (16.5)	18.2 (14.2)	164 (37.2)
Range	65.4–163	1.5–7.0	677–1860	28.2–77.6	6.16–46.2	106–241
CV%	32.8	38.5	35.7	35.7	78.1	22.7
Intact LDX						
Mean (SD)	47.9 (18.6)	1.0 (0.3)	60.7 (21.0)	2.5 (0.9)	0.0 (0.0)	1900 (340)
Range	24.8–79.3	1.0–2.0	36.2–99.9	1.5–4.2	0.0–0.0	1220–2350
CV%	38.8	28.5	34.6	34.6	–	17.9

*Median

$AUC_{0–24}$ = area under the drug concentration-time curve from 0 to 24 hours; C_{avg} = average concentration at steady state; $C_{max,ss}$ = maximum observed drug concentration at steady state; CV% = coefficient of variation; FI = fluctuation index; LDX = lisdexamfetamine dimesylate; SD = standard deviation; T_{max} = time to maximum drug concentration

is eliminated from the serum by 5 hours post-dose, and d-amphetamine is 95% eliminated by approximately 48 hours post-dose.

Adverse events

One participant was withdrawn from the study due to tachycardia after receiving one dose of LDX 70 mg. The baseline pulse in this individual was approximately 2 standard deviations higher than the average obtained in this study population. Eleven (92%) of the 12 participants reported one or more AEs during the study (Table 4). Most frequently reported AEs were anorexia, insomnia, and tachycardia, all commonly observed with amphetamine agents. Most frequently reported TEAEs were anorexia, insomnia, tachycardia, hyperkinesia, headache, euphoric mood, abdominal pain, and upper respiratory tract infection. Ten (16%) of the 64 reported TEAEs were deemed unrelated to the study medication. All other AEs were rated as possibly related (8/64, 13%) or probably related (46/64, 72%) to study medication. Forty-eight percent (31/64) of the TEAEs were mild in severity, 50% (32/64) were moderate, and 2% (1/64; anorexia) were severe. Of the 32 moderate TEAEs, 28 were deemed possibly or probably related to study medication. The majority (52/64, 81%) of TEAEs occurred during the dosing period. No deaths or serious AEs occurred.

Compared with pre-dose measurements on the morning of day 7, systolic blood pressure appeared to have a mean increase of 7 to 9 mmHg between 2 and 4 hours post-dose, and diastolic blood pressure appeared to have a maximum mean increase of 4 to 8 mmHg from 1 to 4 hours post-dose. There were no visible trends in ECG abnormalities. No laboratory abnormalities were reported as AEs by the investigator.

Table 4. *Adverse events occurring in ≥ 25% of subjects (*n *= 12)*

Adverse event	Subjects reporting, *n* (%)
Any event	11 (92)
Anorexia	7 (58)
Insomnia	6 (50)
Tachycardia	5 (42)
Hyperkinesia	4 (33)
Abdominal pain	3 (25)
Euphoric mood	3 (25)
Headache	3 (25)
Upper respiratory tract infection	3 (25)

Discussion

In this phase 1 study, once-daily doses of LDX 70 mg produced steady-state concentrations of d-amphetamine in healthy adults by day 5. By 5 hours after the final dose on day 7 there were no detectable LDX levels. Elimination of 95% of active d-amphetamine occurred approximately 48 hours after the final dose on day 7.

No unexpected accumulation in parent compound or active ingredient occurred at steady state. The AUC of intact LDX was approximately 5% that of d-amphetamine. However, it should be noted that this study evaluated fasting pharmacokinetics only, with no food given 10 hours before the study dose until 4 hours after dosing on the morning of sampling. Unlike MAS XR, food does not have a significant effect on d-amphetamine or LDX bioavailability in healthy

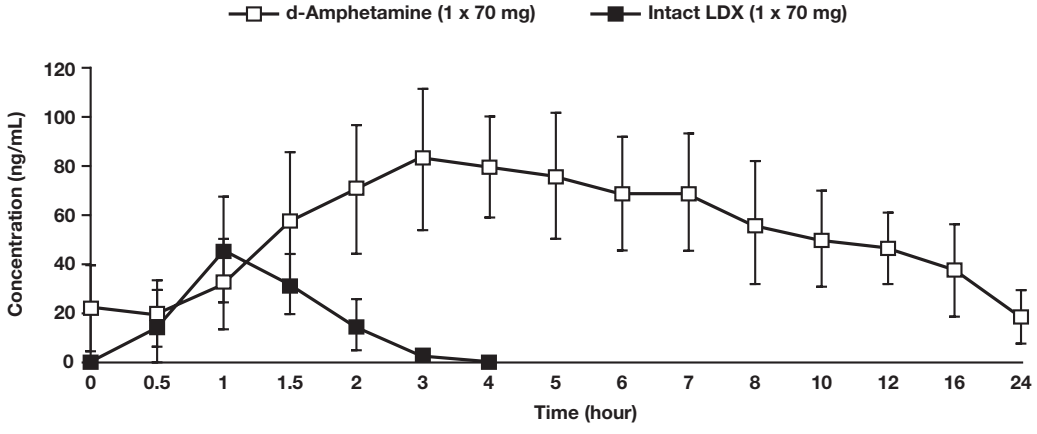

Figure 1. *Steady-state plasma drug concentration-time plot (fasted); d-amphetamine and intact LDX following day 7 drug administration. LDX = lisdexamfetamine dimesylate*

adults[14,15]. AUC_{0-24} and C_{max} for d-amphetamine and AUC_{0-24} for intact LDX were similar when LDX 70 mg was administered to healthy adults in the fed or fasted state, whereas C_{max} for intact LDX was lower when administered with food. The T_{max} of d-amphetamine and intact LDX was about 1 hour longer when taken with food (Krishnan S, Zhang Y, manuscript in preparation).

Additionally, it has been observed that LDX is capable of more consistent delivery of d-amphetamine in children aged 6 to 12 years with ADHD. In a clinical study comparing bioequivalent doses of LDX and MAS XR with placebo in children with ADHD, subjects treated with LDX achieved a median peak d-amphetamine plasma concentration in 4.5 hours, with a range of 4.5 to 6.0 hours and a CV% of 15.55. In contrast, subjects treated with MAS XR achieved a median peak d-amphetamine plasma concentration in 6.0 hours with a range of 3.0 to 12.0 hours and a CV% of 52.77.

The AEs noted in this study were those commonly observed with stimulant therapy[15,16]. One patient was withdrawn from the study because of tachycardia. In short-term and long-term extension clinical trials of LDX in children with ADHD aged 6 to 12 years, the most frequently observed AEs were decreased appetite, insomnia, and irritability. No serious AEs were observed and there were no clinically relevant cardiovascular findings[11–13]. The pharmacokinetic profile of the pro-drug LDX is consistent with that observed with long-acting, formulated stimulants. For example, after a 7-day treatment course of MAS XR 30 mg once daily, the steady state for d- and l-amphetamine was 67 and 22 ng/mL, respectively, with a T_{max} of 4 hours[16]. These data suggest that LDX may be able to provide long-acting effects.

This study had several limitations, including its open-label design and its small sample size. However, since this study was designed to assess pharmacokinetic profiles over time in healthy volunteers, a larger sample size was deemed unnecessary. Moreover, since it was not a clinical trial, its open-label design should not be problematic.

Conclusion

In conclusion, once-daily administration of oral LDX 70 mg produced steady-state concentrations of d-amphetamine by day 5, and intact LDX fell below detectable levels within approximately 6 hours after the final dose on day 7. The observed AEs in this population of healthy adults are consistent with those of currently available amphetamine therapies. LDX will be further assessed for clinical efficacy and safety in comparison with placebo and other agents in patients diagnosed with ADHD.

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