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A Single-Dose, Open-Label Study of the Pharmacokinetics, Safety, and Tolerability of Lisdexamfetamine Dimesylate in Individuals With Normal and Impaired Renal Function

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Background: Lisdexamfetamine (LDX) and D-amphetamine pharmacokinetics were assessed in individuals with normal and impaired renal function after a single LDX dose; LDX and D-amphetamine dialyzability was also examined.

Methods: Adults (N = 40; 8/group) were enrolled in 1 of 5 renal function groups [normal function, mild impairment, moderate impairment, severe impairment/end-stage renal disease (ESRD) not requiring hemodialysis, and ESRD requiring hemodialysis] as estimated by glomerular filtration rate (GFR). Participants with normal and mild to severe renal impairment received 30 mg LDX; blood samples were collected predose and serially for 96 hours. Participants with ESRD requiring hemodialysis received 30 mg LDX predialysis and postdialysis separated by a washout period of 7–14 days. Predialysis blood samples were collected predose, serially for 72 hours, and from the dialyzer during hemodialysis; postdialysis blood samples were collected predose and serially for 48 hours. Pharmacokinetic end points included maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) or to last assessment (AUC_{last}).

Results: Mean LDX C_{max}, AUC_{last}, and $AUC_{0-\infty}$ in participants with mild to severe renal impairment did not differ from those with normal renal function; participants with ESRD had higher mean C_{max} and AUC_{last} than those with normal renal function. D-amphetamine exposure (AUC_{last} and $AUC_{0-\infty}$) increased and C_{max} decreased as renal impairment increased. Almost no LDX and little D-amphetamine were recovered in the dialyzate.

Conclusions: There seems to be prolonged D-amphetamine exposure after 30 mg LDX as renal impairment increases. In individuals with severe renal impairment (GFR: $15 \leq 30$ mL·min^{-1}·1.73 m^{-2}), the maximum LDX dose is 50 mg/d; in patients with ESRD (GFR: <15 mL·min^{-1}·1.73 m^{-2}), the maximum LDX dose is 30 mg/d. Neither LDX nor D-amphetamine is dialyzable.

Key Words: renal impairment, lisdexamfetamine dimesylate, pharmacokinetic, hemodialysis, D-amphetamine

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Lisdexamfetamine (LDX), a D-amphetamine prodrug, is approved in the United States and other countries for the treatment of attention-deficit/hyperactivity disorder (ADHD) in individuals aged 6 years and older and only in the United States for adults with moderate to severe binge eating disorder.[1] After absorption, which occurs through carrier-mediated transport in the small intestine, LDX is metabolized in red blood cells into D-amphetamine and L-lysine.[2] LDX and amphetamine are later excreted primarily in the urine, with D-amphetamine accounting for nearly half of the excretion product.[3] The urinary excretion of amphetamine is pH dependent, with acidic urine resulting in a higher excretion rate and alkaline urine resulting in a lower excretion rate.[4,5] Of note, the higher excretion rate of amphetamine in acidic urine may be because it is a weak base[6] and is therefore ionized in acidic conditions. Deionized amphetamine is passively reabsorbed by the kidney and, under acidic conditions, amphetamine is ionized so that less is reabsorbed by the kidney, resulting in a higher excretion rate.[4]

The pharmacokinetic profile of LDX has been examined across a range of doses in healthy children and adults.[3,7–9] In healthy adults, LDX produces a dose-proportional D-amphetamine pharmacokinetic profile at doses ranging from 50 to 250 mg.[7] More specifically, within a therapeutic dose range (50–70 mg LDX), mean maximum D-amphetamine concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$) range from approximately 44 to 80 ng/mL and approximately 818–1349 ng·h^{-1}·mL^{-1}, respectively, in healthy adults.[3,7,9,10]

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In addition, interindividual and intraindividual variability in C_{max} and $AUC_{0-\infty}$ for D-amphetamine are low, suggesting consistent delivery of D-amphetamine after conversion from LDX in healthy adults.[7]

In a previously published study, D-amphetamine clearance after a single 50-mg dose of LDX was found to decrease with age in older, healthy individuals.[11] Although a clear relationship between renal function, as measured by baseline creatinine clearance rates, and D-amphetamine clearance was not found in that study,[11] another study has reported that creatinine clearance was strongly correlated with D-amphetamine exposure after D-amphetamine administration in individuals who had experienced a cerebral infarct.[12] Therefore, the relationship between renal function and D-amphetamine exposure remains unclear.

However, it is clear that amphetamine excretion is mediated primarily through renal systems and is highly dependent on urinary pH.[13–15] Under acidic urinary conditions, more than 70% of amphetamine is excreted unchanged in the urine, whereas less than 5% is eliminated unchanged when urinary pH is basic.[13,14] Given the important role of the renal system in regulating amphetamine excretion and the lack of data on the impact of renal impairment on amphetamine pharmacokinetics, a better understanding of the effects of compromised renal function on the pharmacokinetics of LDX and D-amphetamine could help determine whether dose modifications are warranted in populations with clinically meaningful renal impairment. Because renal impairment can occur with a variety of medical conditions and might necessitate the need for dose adjustment, an expert panel has recommended that the pharmacokinetics of all renally eliminated drugs be tested in individuals with chronic kidney disease and that hemodialysis clearance be evaluated for drugs that may be used in patients with end-stage renal disease (ESRD).[16]

The primary objective of this study was to assess the pharmacokinetics of LDX and D-amphetamine in individuals with normal renal function and varying degrees of renal impairment after a single 30-mg dose of LDX using noncompartmental methods. In the interest of safety, the 30-mg dose was chosen for this study because it is the recommended starting dose of LDX for the treatment of ADHD.[1] Secondary objectives included the evaluation of the dialyzability of LDX and D-amphetamine, which has implications for all D-amphetamine–based medications, and the assessment of the safety and tolerability of LDX in individuals with normal renal function and varying degrees of renal impairment.

MATERIALS AND METHODS

Study Design

This single-dose, open-label pharmacokinetic study was conducted at 2 centers in the United States in participants with normal renal function and varying degrees of renal impairment. The protocol was approved by the institutional review board of the study sites before study initiation, and the study was conducted in accordance with the International Conference on Harmonisation and Good Clinical Practice and with the Declaration of Helsinki. All participants received a complete study description and provided written informed consent before the study.

Participants

Eligible participants were enrolled in 1 of 5 renal function groups on day 1 or day 2, as estimated by glomerular filtration rate (GFR) determined by the Modification of Diet in Renal Disease (MDRD) study equation.[17] These 5 renal function groups consisted of, respectively, those with normal renal function (GFR: $\geq$90 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), mild renal impairment (GFR: 60–89 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), moderate renal impairment (GFR: 30–59 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), severe renal impairment [GFR: 15–29 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ or ESRD (GFR: $<15\ mL^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$) not requiring hemodialysis], and ESRD requiring hemodialysis. Up to 8 participants were to be enrolled in each group (N = 40) to ensure that at least 5 participants in each group completed the study.

All eligible adults (18–85 years of age) were healthy men or nonpregnant, nonlactating women with stable renal function based on 2 measurements of serum creatinine separated by at least 7 days (one of which could have been a historical value within the last 3 months). Renal function was considered stable if the serum creatinine values differed by $\leq$30% of the lower value, although this criterion was not applicable to participants with ESRD. In situations in which the calculated renal function estimated by the MDRD formula was judged inaccurate by the investigator, a 24-hour urine collection could be performed to obtain a more accurate estimation. This 24-hour urine collection estimation became the reference value characterizing the participant's renal function. In addition, all eligible participants had a body mass index (BMI) from 18.5 to 40.0 kg/m^2 at screening; had hemoglobin values of $\geq$9 g/dL at screening and on day 1/day 2 of the treatment period and, for those with ESRD requiring hemodialysis, on day 1/day 2 of treatment period 1 (prehemodialysis); had no clinically significant or relevant medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), or laboratory evaluation other than those associated with the impaired renal function; were not taking medications (including over-the-counter multivitamins, herbals, or homeopathics) that could interfere with the action, absorption, or disposition of LDX (medications that were not permitted included urinary acidifying agents [eg, ammonium chloride, sodium acid phosphate], urinary alkalinizing agents [eg, acetazolamide, some thiazides], and monoamine oxidase inhibitors); and had the ability to understand and fully comply with study procedures and to provide consent.

Participants were excluded if they had a current or recurrent comorbid disease other than those associated with the impaired renal function that could affect the pharmacokinetics or pharmacodynamics of LDX or if they had intolerance or hypersensitivity to the study drugs or related compounds. Additional exclusion criteria included, for those with normal renal function, a history or presence of medical or psychiatric disorders that required treatment and made the participant unlikely to complete the study or that presented undue risk from the study drug or procedures; for those with impaired renal function, a concurrent chronic or acute illness or unstable medical condition (other than those associated with their renal disease) that may have deteriorated and

confounded the safety assessments, increased risk to the participant, or led to difficulty complying with the study protocol; an acute illness within 14 days of the study dose or current use (within the last 30 days) of any medication (prescriptions, over the counter, herbal, or homeopathic preparations) that could affect the condition being studied, the pharmacokinetics or pharmacodynamics of the study drug, or the clinical and laboratory assessments; a history or presence of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, transient ischemic attacks, or other serious cardiac problems; family history of sudden cardiac death or ventricular arrhythmia; a history of uncontrolled moderate to severe hypertension or a resting sitting systolic blood pressure >149 mm Hg or diastolic blood pressure >90 mm Hg; a history of thyroid disease that had not been stabilized within 3 months of screening; history of seizures; being considered a risk for suicide; a history of substance abuse or dependence disorder within 6 months of the time of screening or a lifetime history of amphetamine, cocaine, or other stimulant abuse; consumption of >3 units/day (men) or >2 units/day (women) of alcohol; consumption of >10 cigarettes/day; having donated blood within 60 days of the first dose of study drug or plasma within 14 days; use of another investigational product within 30 days of receiving the first dose of study drug; active enrollment in another clinical study; and showing substantial changes in eating habits within 30 days of receiving the first dose of study drug, the inability to follow a standardized diet and meal schedule, or the inability to fast.

Treatment

For each treatment period, participants were administered 30 mg LDX in an open-label fashion orally with 240 mL of room temperature water on day 1 of the treatment period; LDX had to be swallowed whole. As noted previously, in the interest of safety, the 30-mg dose was chosen for this study because it is the recommended starting dose of LDX for the treatment of ADHD.[1] Participants were required to fast for approximately 10 hours before LDX administration through 4 hours postdose after the scheduled pharmacokinetic samples were collected.

For participants with normal renal function or mild to severe renal impairment (those who did not require hemodialysis), the study consisted of a 28-day screening phase and a single-dose 5-day treatment period. For participants with ESRD requiring hemodialysis, the study consisted of a 28-day screening phase and 2 treatment periods (a 3-day predialysis single-dose treatment period and a 4-day single-dose postdialysis treatment period); treatment periods were separated by a 7- to 14-day washout period. In all renal groups, a follow-up telephone call was made 7–10 days after the last dose to identify ongoing and/or new adverse events (AEs) and concomitant medications taken since the last dose of study drug.

Pharmacokinetic Measurements

Blood samples for pharmacokinetic analyses were collected predose and serially for 96 hours postdose for participants with normal renal function and those in renal impairment groups not requiring hemodialysis. In participants with ESRD requiring hemodialysis, during treatment period 1 (prehemodialysis), blood samples for pharmacokinetic analyses were collected predose and serially for 72 hours postdose; blood samples were also collected from the dialyzer's arterial and venous lines during hemodialysis (4–7 hours postdose) and for 1 hour posthemodialysis (8 hours postdose). Dialyzate samples were collected 4–7 hours postdose. During treatment period 2 (posthemodialysis), blood samples were collected predose and serially for 48 hours.

Pharmacokinetic analyses were conducted using noncompartmental methods. The pharmacokinetic parameters that were calculated included the time of maximum observed concentration sampled during a dosing interval (t_{max}), the maximum plasma concentration (C_{max}), $AUC_{0-\infty}$, AUC from time 0 to the last measurable concentration (AUC_{last}), and the terminal half-life ($t_{½}$). Additional calculated pharmacokinetic parameters included the first-order rate constant associated with the terminal (log-linear) portion of the curve (λ_z), total body and weight-corrected clearance for extravascular administration divided by the fraction of dose absorbed (CL/F and CL/F/kg), and the total and weight-corrected volume of distribution associated with the terminal slope after extravascular administration divided by the fraction of dose absorbed (V_z/F and V_z/F/kg). Pharmacokinetic parameters calculated from the dialyzate samples also included the dialysis clearance (CL_D) calculated from the arterio- and venous-line concentrations and the CL_D calculated for the drug recovery in dialyzate fluid (CL_{DR}).

CL_D for LDX and D-amphetamine was calculated using the following equation: $CL_D = [(C_A–C_V)/C_A] \times Q_b \times (1\text{-Hct})$. In this equation, C_A and C_V are the LDX and D-amphetamine plasma concentrations in the dialyzer arterio and venous lines, respectively; Q_b is the blood flow rate through the dialyzer; Hct is the hematocrit; and $Q_b \times (1\text{-Hct})$ represents the plasma flow rate through the dialyzer. CL_D was also calculated for each analyte using the recovery method (CL_{DR}) with the following equation: $CL_{DR} = A_{dialyzate}/AUC_{plasma}$, where $A_{dialyzate}$ is the total amount of LDX or D-amphetamine recovered in the dialyzate and AUC_{plasma} is the AUC calculated for the C_A plasma concentration.

Bioanalytical Methods

The plasma concentrations of LDX and D-amphetamine were measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods similar to those reported in previous publications.[7,11] Specifically, 50 μL of internal standard was added to a 100-μL aliquot of plasma for analysis. Then, the proteins were precipitated by the addition of 500 μL of a chilled acetonitrile:formic acid (100:5; vol:vol) solution. After vortexing and centrifugation, the supernatant was removed and evaporated under nitrogen at 40°C and reconstituted to 300 μL. A 10-μL sample was injected into the LC-MS/MS 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 (Albany Molecular Research, Inc., Albany, NY; Alsachim, Illkirch-Graffenstaden, France) and from 2 to 200 ng/mL for D-amphetamine (Cerilliant Corp., Round Rock, TX). 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. Table 1 summarizes the plasma concentration assay characteristics.

Dialyzate concentrations of LDX and D-amphetamine were measured using ultraperformance LC-MS/MS (UPLC-MS/MS) methods. Specifically, 50 μL of internal standard was added to a 300-μL aliquot of dialyzate for analysis. After vortexing the samples for 1 minute at high speed, 350 μL of 50 mM ammonium acetate was added to each sample. The samples were then placed in a Quadra 4 (Tomtec Life Sciences, Hamden, CT) pipetting system for solid phase extraction; extracted samples were collected in a 96-well collection plate. Then, the collection plate was placed in a TurboVap LV evaporator (Biotage, Charlotte, NC) for evaporation under nitrogen at 40°C. A 200-μL aliquot of reconstitution solution was then added to each sample; 5 μL of the sample was then injected into a UPLC-MS/MS system, which consisted of an API-4000 mass spectrometer (AB SCIEX, Framingham, MA) coupled with a Waters UPLC system (Waters Corporation, Milford, MA).

The dialyzate concentrations were calculated using an 8-point standard curve. The lower limit of quantification was 0.05 ng/mL for LDX and 0.1 ng/mL for D-amphetamine; calibration standards in human plasma ranged from 0.05 to 10 ng/mL for LDX (Cerilliant Corp., Alsachim) and from 0.1 to 20 ng/mL for D-amphetamine (Cerilliant Corp.,). Quality control samples for LDX (0.15, 1, and 8 ng/mL) and D-amphetamine (0.3, 2, and 16 ng/mL) were prepared in separate batches and stored at −20°C. **Supplemental Digital Content 1** (see **Table**, http://links.lww.com/TDM/A138) also summarizes the dialyzate assay characteristics.

During the analysis of the participants with ESRD requiring hemodialysis, human dialyzate was used in the matrices. In samples from these participants, large variations in LDX concentrations were observed during sample reassay and incurred sample reproducibility evaluation. After an investigation, it was concluded that these variations resulted from a factor in the samples that caused a matrix effect. Although no matrix effects had been observed during validation, the dialyzate plasma used during validation for the ESRD group was from participants whose renal function impairment was not as severe as that of participants with ESRD because this type of plasma is rare and difficult to obtain. Based on assessment samples from participants with normal renal function and less severe renal impairment (ie, those with mild, moderate, or severe renal impairment), the analytical method for quantifying LDX was determined to be accurate and robust.

Safety and Tolerability Measurements

AEs, vital signs, 12-lead ECGs, physical examinations, and clinical laboratory tests were monitored during the study. AEs were recorded from the time of informed consent, throughout all treatment periods, and at follow-up; AEs were classified according to their severity and relationship to the study drug. Physical examinations and clinical laboratory evaluations were performed at screening and on days 1 and 5 (on day 4 in participants with ESRD requiring hemodialysis) of the treatment period for all groups not requiring hemodialysis; for the ESRD group requiring hemodialysis, assessments were made at screening and on day 4 of treatment period 1 and on days 1 and 3 of treatment period 2. Vital sign assessments were conducted at screening, day 1, and days 1–5 (30 minutes predose and 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours postdose) for all groups not requiring hemodialysis; for the ESRD hemodialysis group, assessments were made at screening and days 1–4 of treatment period 1 (30 minutes predose and 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours postdose) and at day 1 and days 1–3 (30 minutes predose and 1, 2, 4, 12, 24, and 48 hours postdose) during treatment period 2. ECGs were conducted at screening, on day 1, day 1 (30 minutes predose and 4 hours postdose), and day 5 (96 hours postdose)

TABLE 1. Baseline Demographic Characteristics by Renal Function Group, Safety Analysis Set

	Normal (n = 8)	Mild (n = 8)	Moderate (n = 8)	Severe* (n = 8)	ESRD (n = 8)	Total (N = 40)
Mean ± SD age, yrs	62 ± 6.0	63 ± 7.9	66 ± 8.3	66 ± 7.3	51 ± 9.0	62 ± 9.3
Sex, n (%)						
Men	2 (25.0)	2 (25.0)	7 (87.5)	5 (62.5)	7 (87.5)	23 (57.5)
Women	6 (75.0)	6 (75.0)	1 (12.5)	3 (37.5)	1 (12.5)	17 (42.5)
Race, n (%)						
White	6 (75.0)	7 (87.5)	7 (87.5)	5 (62.5)	0 (0)	25 (62.5)
Black	2 (25.0)	1 (12.5)	1 (12.5)	3 (37.5)	8 (100.0)	15 (37.5)
Ethnicity, n (%)						
Hispanic or Latino	3 (37.5)	3 (37.5)	5 (62.5)	5 (62.5)	1 (12.5)	17 (42.5)
Not Hispanic or Latino	5 (62.5)	5 (62.5)	3 (37.5)	3 (37.5)	7 (87.5)	23 (57.5)
Mean ± SD (weight, kg)	68.91 ± 5.619	72.03 ± 7.682	84.53 ± 11.380	92.80 ± 17.090	98.35 ± 21.657	83.32 ± 17.605
Mean ± SD (height, cm)	166.31 ± 8.345	162.09 ± 5.467	173.81 ± 9.102	166.06 ± 10.428	178.50 ± 6.676	169.36 ± 9.820
Mean ± SD (BMI, kg/m^2)	25.1 ± 3.29	27.4 ± 2.77	27.9 ± 1.77	33.5 ± 4.25	30.7 ± 6.20	28.9 ± 4.77

*Participants in the severe renal impairment group may have ESRD but do not require hemodialysis.

for all groups not requiring hemodialysis; for the ESRD hemodialysis group, assessments were conducted at screening, day 1 (30 minutes predose and 3 hours postdose), and day 4 (72 hours postdose) during treatment period 1 and on day 1, day 1 (30 minutes predose and 4 hours postdose), and day 3 (48 hours postdose) during treatment period 2.

Statistical Analysis

Pharmacokinetic analyses were based on the pharmacokinetic analysis set (all participants in the safety analysis set for whom the primary pharmacokinetic data were considered sufficient and interpretable); all analyses were conducted using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, CA). Pharmacokinetic parameters by renal function group and plasma concentration at each sampling time were summarized using descriptive statistics; inferential statistics were not conducted because of the small sample sizes. Regression analyses between pharmacokinetic parameters and renal function (calculated using the MDRD[17] and the Cockroft–Gault[18] equations) were performed across renal function groups for each analyte. Steady-state D-amphetamine concentrations at LDX doses of 30, 50, and 70 mg were simulated using nonparametric superposition for participants with normal renal function and severe renal impairment. Values for C_{max} and AUC_{tau} (AUC for the defined interval between doses) were calculated from the simulated steady-state concentrations for each renal function group and dose level. Linear dose proportionality was assumed for both groups.

The safety analysis set included participants who received at least 1 dose of the study drug and had ≥1 postdose safety assessment. All safety end points were summarized using descriptive statistics.

RESULTS

Participant Disposition and Demographics

Of the 68 screened participants, 40 were enrolled in the study; all enrolled participants completed the study and were included in the safety analysis and pharmacokinetic analysis sets. Demographics for the safety analysis set are summarized in Table 1. The overall mean ± SD age was 61.6 ± 9.25 years (range, 40–76 years); most of the participants were white (25/40; 62.5%) and male (23/40; 57.5%). The ESRD group was younger than all other renal function groups, and all participants in the ESRD group were black in contrast to the other renal function groups in which a majority of participants were white. Most of the participants with normal renal function or mild renal impairment were women, whereas most of the participants in the other renal function groups were men. Participants in the severely impaired and ESRD groups had higher BMIs than those in the other renal function groups.

Pharmacokinetic Measurements

LDX Pharmacokinetics

Figure 1A shows linear scale plasma concentrations over time by renal function group for LDX; descriptive statistics for all pharmacokinetic parameters for LDX by renal function group are summarized in Table 2. In general, plasma concentration curves were similar for participants with normal renal function and those with mild, moderate, or severely impaired renal function. In these groups, peak mean plasma LDX concentrations were observed at 1 hour and were below the detectable limit at 4–6 hours postdose. Although peak mean plasma LDX concentrations were observed at 1.5 hours postdose in participants with ESRD, peak LDX levels were maintained over a longer period in participants with ESRD than those in participants from the other renal groups (Fig. 1A, inset). Peak LDX levels in participants with ESRD tended to decline by 24 hours postdose. However, because of the large variations in LDX concentration in the ESRD group, levels of LDX were still detectable at 30, 48, and 72 hours postdose. It was concluded that this was caused by a factor in the plasma samples that were used in this study; the factor resulted in a matrix effect, so the data from the ESRD group must be cautiously interpreted.

Pharmacokinetic parameters (Table 2) for LDX were similar between the normal renal function group and the mild, moderate, and severely impaired renal function groups. Mean C_{max}, AUC_{last}, and $AUC_{0-\infty}$ for LDX were not substantially different in participants with mild, moderate, or severely impaired renal function compared with the normal function group after 30 mg LDX; median t_{max} and $t_{½}$ were also generally similar among these groups. Mean CL/F/kg was reduced in participants with severe renal impairment compared with the normal function group. In the ESRD group, C_{max} and AUC_{last} were higher than those in the normal function group.

D-Amphetamine Pharmacokinetics

Figure 1B shows linear scale plasma concentrations over time by renal function group for D-amphetamine; descriptive statistics for all D-amphetamine pharmacokinetic parameters by renal function group are summarized in Table 2. D-amphetamine concentration curves were similar across renal function groups; however, peak concentrations were lower in the ESRD group relative to the rest of the renal function groups. In the normal renal function group and mild, moderate, and severely impaired renal function groups, mean plasma D-amphetamine concentrations peaked at approximately 4 hours postdose and returned to approximately predose levels from 72 to 96 hours postdose. In the ESRD group, mean plasma concentrations were similar during each treatment, with the mean plasma concentrations peaking at 4 hours postdose and declining to predose levels at 48–72 hours.

For D-amphetamine, C_{max} decreased and AUC_{last} and $AUC_{0-\infty}$ increased as the level of renal impairment increased (Table 2). The mean exposure (AUC_{last} and $AUC_{0-\infty}$) was highest and mean C_{max} was lowest among participants with severe renal impairment and ESRD. Median $t_{½}$ increased with increasing renal impairment, with the shortest duration observed in participants with normal function and the longest observed in those with ESRD. Mean $CL \cdot F \cdot kg$ was lowest among participants in the ESRD group, with this group having an approximate 50%

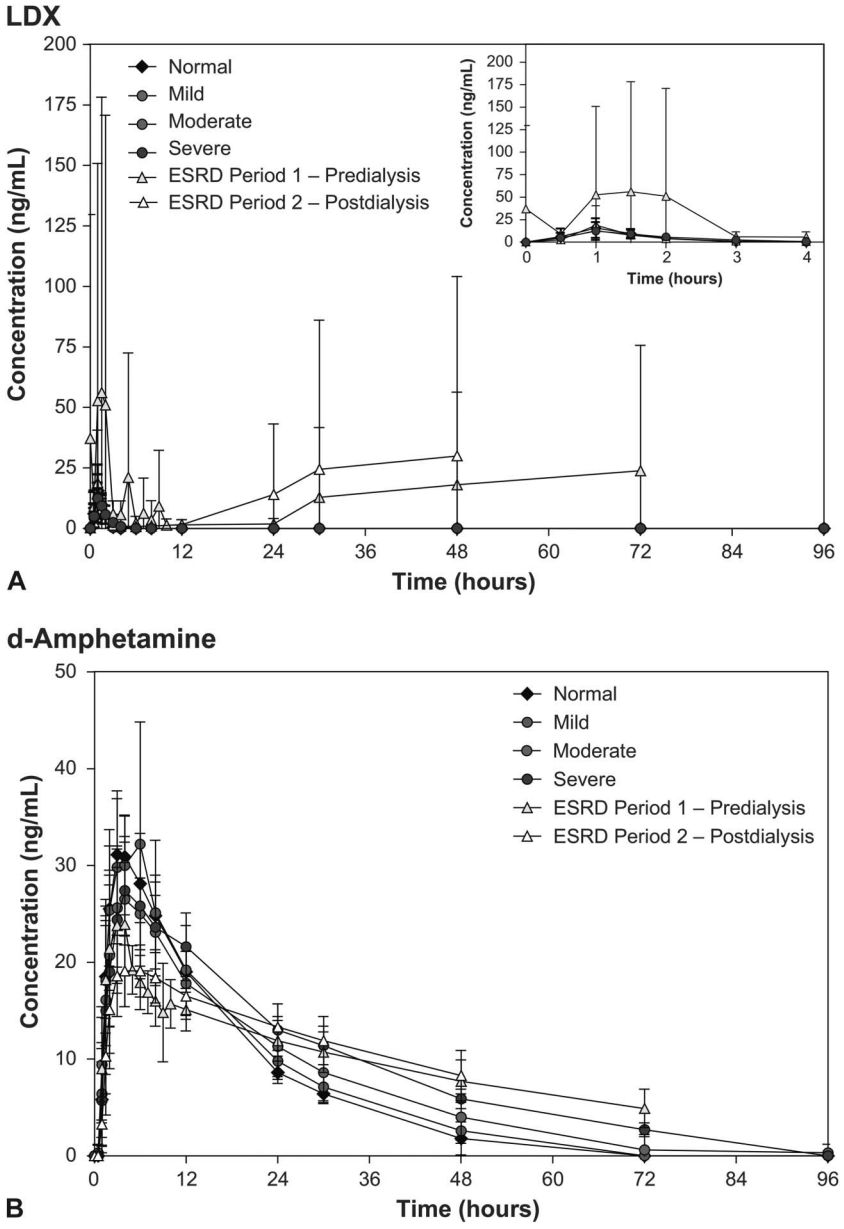

FIGURE 1. Mean ± SD LDX plasma concentrations (inset from time 0 to 4 hours) (A) and D-amphetamine plasma concentrations (B) by renal function group, pharmacokinetic analysis set.

reduction in total body clearance. Median t_{max} was similar in all the groups (range, 3.3–4.3). No substantial differences were observed between prehemodialysis and posthemodialysis assessments in the ESRD group.

Relationship of Pharmacokinetics to Renal Function

Lisdexamfetamine

For LDX, there were no strong correlations observed between renal function and any of the pharmacokinetic parameters measured when the MDRD or Cockcroft–Gault equations were used to estimate renal function ($R^2 \leq 0.1$ for all parameters). Although clearance was reduced in participants with severe renal impairment and in those with ESRD, LDX was adequately cleared in these participants.

D-Amphetamine

For D-amphetamine, negative correlations were found between renal function and $AUC_{0-\infty}$ [$R^2 = 0.404$ (Cockroft–Gault) and 0.3631 (MDRD)] and weight-adjusted CL/F [$R^2 = 0.5933$ (Cockroft–Gault) and 0.6708 (MDRD)]; this was mostly due to participants who had a renal function value <30 mL/min. There were no strong correlations between C_{max} and renal function [$R^2 = 0.077$ (Cockroft–Gault) and 0.1268 (MDRD)]. Scatter plots depicting correlations between renal function and C_{max} and weight-adjusted CL/F are depicted in Figure 2A through 2D.

Dialyzability

The results of the pharmacokinetic analysis for LDX and D-amphetamine in the dialyzate from the ESRD group

TABLE 2. Mean ± SD Pharmacokinetic Parameters by Renal Function Group, Pharmacokinetic Analysis Set

	Renal Function	C_{max}, ng/mL*	t_{max}, h*	AUC_{last}, ng·h/mL*	$AUC_{0-\infty}$, ng·h/mL	λ_z, h^{-1}
LDX	Normal	15.7 ± 3.3	1.1 ± 0.2	17.5 ± 4.5	23.7 ± 3.9†	1.4 ± 0.2†
	Mild	16 ± 10.5	1.1 ± 0.4	16.7 ± 12.6	31.4 ± 24.5†	1.1 ± 0.5†
	Moderate	12.8 ± 3.7	1 ± 0	15.5 ± 5.9	17.9 ± 6.4‡	1.1 ± 0.2‡
	Severe	13.9 ± 9	1.5 ± 0.7	19.2 ± 10	28.6 ± 6.4§	1.2 ± 0.3§
	ESRD—dose predialysis	60.7 ± 120.3	1.1 ± 0.2	1244.3 ± 2768.9	24 ± 2.8†	1.1 ± 0.5†
	ESRD—dose postdialysis	37.7 ± 71	9.8 ± 17.4	864.5 ± 2094.1	NA¶	NA¶
D-Amphetamine	Normal	32.2 ± 5.3	3.5 ± 0.5	527.9 ± 69.9	597.9 ± 44.5*	0.1 ± 0*
	Mild	35.1 ± 11.1	4.3 ± 1.6	577.1 ± 117.9	637.7 ± 123.8*	0.1 ± 0*
	Moderate	27.5 ± 4.9	3.9 ± 1	610.6 ± 170.7	702.7 ± 182.9*	0 ± 0*
	Severe	28.4 ± 5.9	4.1 ± 1.4	779.5 ± 146.1	856.9 ± 161.5*	0 ± 0*
	ESRD—dose predialysis	25.5 ± 8	3.3 ± 0.7	741.8 ± 134.8	1065.9 ± 360.4*	0 ± 0*
	ESRD—dose postdialysis	20.1 ± 3.3	4.5 ± 2	623.8 ± 102	1126.3 ± 437.9*	0 ± 0*

	$t_{½}$, h	CL/F, L/h	Weight-Corrected CL/F, $L \cdot h^{-1} \cdot kg^{-1}$	V_Z/F, L	Weight-Corrected V_Z/F, L/kg
LDX	0.5 ± 0.1†	1282.7 ± 211.7†	17 ± 2.6†	924.1 ± 263.6†	12.2 ± 3.4†
	0.7 ± 0.3†	1368.9 ± 1065.4†	19.3 ± 16.1†	1612.5 ± 1676†	23.0 ± 24.7†
	0.7 ± 0.1‡	1809.8 ± 484.4‡	20.4 ± 4.7‡	1670.9 ± 377.7‡	18.9 ± 3.1‡
	0.6 ± 0.2§	1094.3 ± 273.4§	13 ± 2.9§	1016.8 ± 504.8§	12.1 ± 5.9§
	0.7 ± 0.3†	1258.2 ± 147†	13.1 ± 1.7†	1202.5 ± 411†	12.5 ± 4.1†
	NA¶	NA¶	NA¶	NA¶	NA¶
D-Amphetamine	12.1 ± 2.5*	50.4 ± 3.8*	0.7 ± 0.1*	878.6 ± 192*	12.7 ± 2.4*
	12.8 ± 2*	48.6 ± 9.3*	0.7 ± 0.1*	895.9 ± 212.2*	12.4 ± 2.6*
	16.8 ± 5.2*	45.6 ± 13.6*	0.5 ± 0.1*	1044.1 ± 171.4*	12.3 ± 1*
	19.8 ± 1.9*	36 ± 6.2*	0.4 ± 0.1*	1031.1 ± 224*	11.1 ± 1.4*
	40.9 ± 16.3*	30.5 ± 8.5*	0.3 ± 0.1*	1667 ± 413.3*	17.5 ± 5*
	38.2 ± 16.5*	29.9 ± 10.5*	0.3 ± 0.2*	1465.6 ± 241.5*	15.3 ± 3*

Participants in the severe renal impairment group may have ESRD but did not require hemodialysis.
*n = 8.
†n = 2.
‡n = 5.
§n = 4.
¶n = 0.
λ^z = first-order rate constant associated with the terminal (log-linear) portion of the curve; $AUC_{0-\infty}$ = area under the concentration versus time curve extrapolated to infinity, calculated using the observed value of the last nonzero concentration; AUC_{last} = area under the concentration versus time curve from the time of dosing to the last measurable concentration; CL/F = total body clearance for extravascular administration divided by the fraction of dose absorbed; NA = statistics not calculable with the available data; t_{max} = time of maximum observed concentration sampled during a dosing interval; $t_{½}$ = terminal half-life; Vz/F = volume of distribution associated with the terminal slope after extravascular administration divided by the fraction of dose absorbed.

revealed that almost no LDX and little D-amphetamine were recovered by hemodialysis. The mean percentage (range) recovered for LDX was 0% below the detectable limit (below detectable limit to 0.1%) and for D-amphetamine was 2.63% (2.18%–3.30%).

Simulated Steady-State D-Amphetamine Levels

Steady-state mean plasma concentration curves for D-amphetamine over time (based on regression analyses) after 30-, 50-, and 70-mg doses of LDX in individuals with normal renal function or severe renal impairment (GFR: ≤29 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) are presented in Figure 3. Simulated pharmacokinetic parameters through the use of superposition methods based on these data are highlighted in Table 3.

Safety and Tolerability End points

The proportion of participants reporting any treatment-emergent AE (TEAE) was 35% (14/40) after administration of 30 mg LDX **Supplemental Digital Content 2** (see **Table**, http://links.lww.com/TDM/A139). All TEAEs were mild to moderate in severity; TEAEs reported by 12/40 (30%) participants were considered related to the study drug. There were no serious or severe TEAEs during the study, no discontinuations from the study due to TEAEs, and no TEAEs leading to death during the study. The most frequently reported TEAEs overall (reported by at least 2 study participants) were feelings of relaxation, dizziness, and increased blood pressure **Supplemental Digital Content 2** (see **Table**, http://links.lww.com/TDM/A139).

The mean ± SD systolic blood pressure, diastolic blood pressure, and pulse rate were similar at baseline for all renal function groups. However, in the ESRD group, pulse was generally higher and blood pressure was generally lower than the other groups. There were minimal differences in change from baseline between the groups after administration of LDX

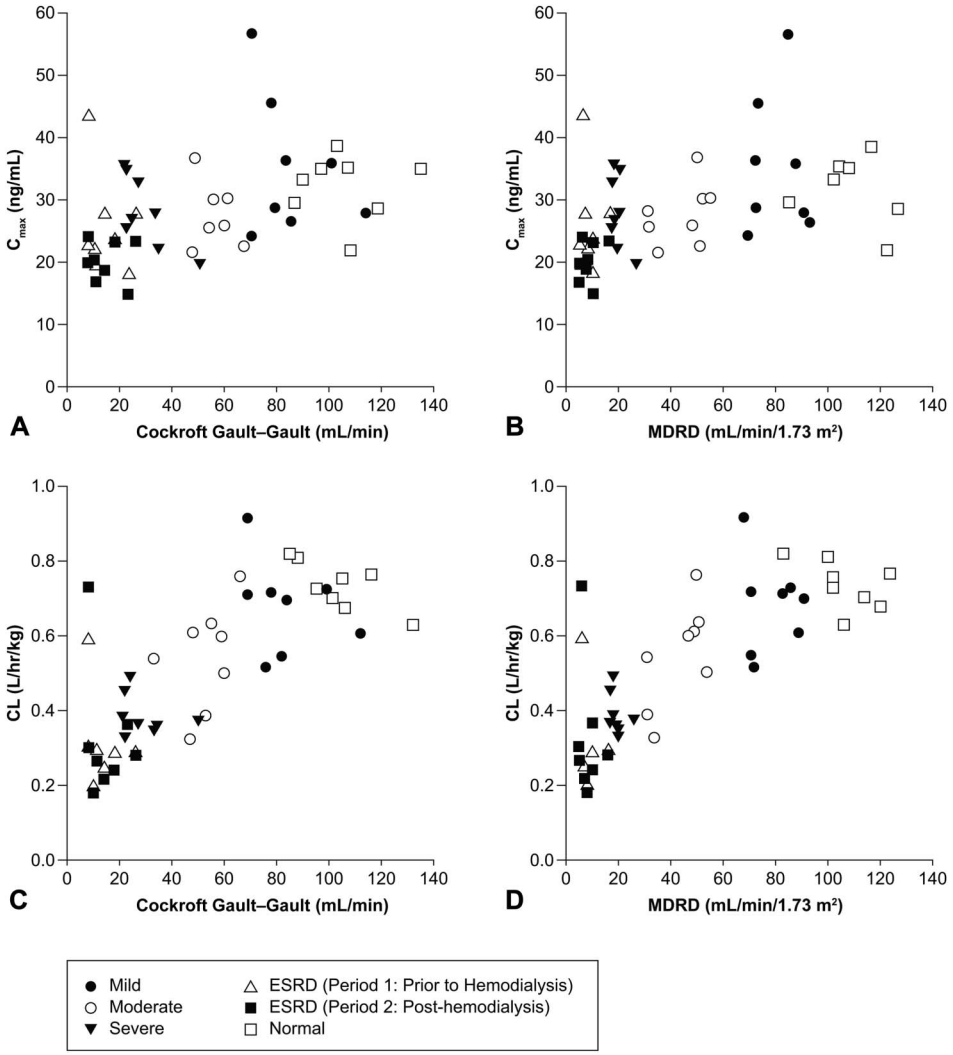

FIGURE 2. Scatter plots depicting correlations between D-amphetamine C_{max} and renal function as measured by the Cockroft–Gault equation (A) and the MDRD equation (B) and between D-amphetamine weight-adjusted CL/F and renal function as measured by the Cockroft–Gault equation (C) and the MDRD equation (D), pharmacokinetic analysis set. CL/F = total body clearance for extravascular administration divided by the fraction of dose absorbed.

(see **Figure**, **Supplemental Digital Content 3**, http://links.lww.com/TDM/A143). In general, changes in vital signs peaked 4–12 hours after treatment before returning to baseline by 96 hours. The mean changes from baseline in ECG heart rates and intervals over time were generally small in magnitude across all renal function groups.

DISCUSSION

Mean C_{max}, AUC_{last}, and $AUC_{0-\infty}$ for LDX in participants with mild, moderate, or severe renal impairment were not substantially different from those observed in participants with normal renal function. Weight-corrected LDX clearance was reduced in participants with severe renal impairment; however, even in participants with severe renal impairment or ESRD, there was still adequate clearance of LDX.

Although participants with ESRD had a higher mean C_{max} and AUC_{last} than those with normal renal function, the magnitude of this effect cannot be determined accurately because LDX concentrations must be interpreted with caution. In the samples from participants with ESRD requiring hemodialysis, large variations in LDX were observed. After an investigation, it was concluded that these variations resulted from a factor in the samples that caused a matrix effect. The matrices used in the analysis were human K_2EDTA plasma and human dialyzate. Although no matrix effects had been observed during validation, the plasma used during validation was from participants whose renal function impairment was not as severe as that of participants with ESRD because this type of plasma is rare and difficult to obtain.

For D-amphetamine, overall exposure (AUC_{last} and $AUC_{0-\infty}$) increased and mean C_{max} decreased as renal impairment increased. Weight-corrected CL/F for D-amphetamine in participants with ESRD was approximately 50% lower than that in participants with normal renal function. These findings and the subsequent simulation findings, which were generally consistent with previously reported C_{max} and $AUC_{0-\infty}$ D-amphetamine pharmacokinetic findings in healthy adults administered the same LDX dose range,[3,7,9] support the recommendation that in individuals with severe renal impairment (GFR: $15 \leq 30$ mL·min^{-1}·1.73 m^{-2}), the maximum LDX dose is 50 mg/d; in patients with ESRD (GFR: <15

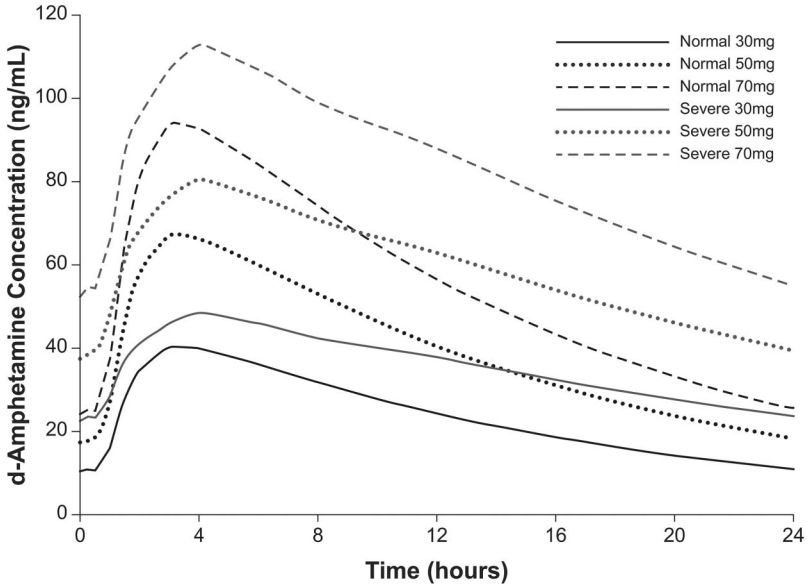

FIGURE 3. Simulated mean steady-state plasma concentration for D-amphetamine in individuals with normal renal function and severe renal impairment (GFR: $\leq$30 mL·min^{-1}·1.73 m^{-2}) after 30-, 50-, and 70-mg doses of LDX based on regression analyses and the data obtained in this study. GFR = glomerular filtration rate.

mL·min^{-1}·1.73 m^{-2}), the maximum LDX dose is 30 mg/d. Neither LDX nor D-amphetamine is dialyzable.

Almost no LDX and little D-amphetamine were recovered in the dialyzate during a normal dialysis session with participants with ESRD. These findings have broad implications for any amphetamine-based medication because they suggest there is little utility in attempting to dialyze D-amphetamine or LDX. This is the first time, to the authors' knowledge, that the dialyzability of d-amphetamine has been systematically investigated.

There were no unexpected changes in vital signs or unexpected TEAEs, no serious or severe TEAEs, and no discontinuations from the study due to TEAEs. All TEAEs were considered mild in severity. The AE profile observed in this study was generally consistent with previously reported studies on the safety of LDX and other amphetamine-based psychostimulants.[19–21]

There are several limitations to this study. Differences in the demographic variables of the participants could potentially limit the generalizability of the results and/or confound the results. For instance, the ESRD group contained all black individuals, whereas all other renal groups were mainly white. In addition, the ESRD group had a higher mean BMI and was younger than those with normal or less severe renal impairment; the severe impairment and ESRD groups included mainly men, whereas the normal function and mild impairment groups were mainly women. However, some of these potential demographic confounds would be minimized because the age and weight were included as factors in the creatinine clearance calculations. In addition, estimates of most LDX pharmacokinetic parameters for the ESRD group before dialysis were based on a limited number of participants and should be interpreted with caution. Similarly, LDX concentrations in individuals with ESRD who required hemodialysis should be interpreted with caution because these data may have large errors due to a factor in the dialyzate samples.

TABLE 3. Simulated Steady-State D-Amphetamine Pharmacokinetic Parameters

Simulated Pharmacokinetic Parameter	Renal Function	LDX Dose, mg		
		30	50	70
C_{max}, ng/mL	Normal	40.4	67.3	94.2
	Severe	48.4	80.7	112.9
AUC_{tau}, ng·h^{-1}·mL^{-1}	Normal	572	953	1335
	Severe	857	1428	1999

AUC_{tau} = area under the concentration versus time curve for the defined interval between doses; C_{max} = maximum plasma concentration.

CONCLUSIONS

There seems to be a prolonged exposure to D-amphetamine as renal impairment increases because of an increase in D-amphetamine $t_{½}$. Therefore, in individuals with severe renal impairment (GFR: 15 $\leq$ 30 mL·min^{-1}·1.73 m^{-2}), the maximum LDX dose is 50 mg/d. In patients with ESRD (GFR: $<$15 mL·min^{-1}·1.73 m^{-2}), the maximum LDX dose is 30 mg/d. Neither LDX nor D-amphetamine is dialyzable; hemodialysis is not recommended for removing D-amphetamine from the bloodstream. Overall, there were no unexpected safety or tolerability findings across individuals with varying degrees of impaired renal function.

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