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An Assessment of the Pharmacokinetics and Tolerability of Single-Ascending Doses of Desvenlafaxine Administered to Healthy Chinese Subjects

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Abstract

Desvenlafaxine (administered as desvenlafaxine succinate) exhibited linear pharmacokinetics after single-dose administration in a US population. The current study assessed the pharmacokinetics and tolerability of single-ascending doses of desvenlafaxine in Chinese subjects. Healthy adult subjects of Chinese descent living in China were randomly assigned to receive either a single dose of desvenlafaxine 50, 100, 200 mg, or placebo in this sponsor-unblinded, inpatient, ascending-dose study. Desvenlafaxine concentrations in urine and plasma were measured using a validated liquid chromatography/tandem mass spectrometry method. Peak plasma concentration (C_{max}) and time to C_{max} (t_{max}) were determined directly from observed data, and area under the plasma concentration-versus-time curve (AUC) was computed. Dose proportionality for C_{max} and AUC was examined using a power model. Tolerability was assessed through adverse event (AE) reporting. Thirty-six subjects were enrolled. The C_{max} of desvenlafaxine increased 138% between the 50 mg (109 ng/mL) and 100 mg (259 ng/mL) doses. The C_{max} for subjects receiving desvenlafaxine 200 mg was 654 ng/mL, a 153% increase compared with the 100 mg dose. The AUC of desvenlafaxine increased 127% from the 50 mg dose (2,520 ng•hr/mL) to the 100 mg dose (5,720 ng•hr/mL), and 126% between the 100 mg and 200 mg (12,900 ng•hr/mL) doses. The power model analysis indicated dose proportionality for AUC, but not for C_{max}. No serious AEs were reported. Desvenlafaxine was generally well tolerated in healthy Chinese subjects, and its exposure (AUC) was dose-proportional. Results from this study and studies in US, European, and Japanese populations indicate that the pharmacokinetics of desvenlafaxine were comparable between these ethnic groups.

Keywords: Desvenlafaxine; Pharmacokinetics; Tolerability

Abbreviations: %CV: Coefficient of Variation; Ae: Amount Excreted; AE: Adverse Event; AUC: Area under the Plasma Concentration-versus-Time Curve; $AUC_{0-\infty}$: Area under the Concentration-time Curve from Time 0 to Infinity; Cl/F: Apparent Oral-Dose Clearance; CL_R: Renal Clearance; C_{max}: Peak Plasma Concentration; CYP: Cytochrome P450; ECG: Electrocardiogram; LC/MS/MS: Liquid Chromatography/Tandem Mass Spectrometry Detection; LOQ: Limit of Quantitation; Max: Maximum; MDD: Major Depressive Disorder; Min: Minimum; NODV: N,O-didesmethylvenlafaxine; NR: Not Reported; ODV: O-desmethylvenlafaxine; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; $t_{1/2}$: Mean Elimination Half-Life; TEAEs: Treatment-Emergent Adverse Events; t_{max}: Time to Peak Plasma Concentration; V_z/F: Apparent Volume of Distribution

Introduction

The hepatic cytochrome P450 (CYP) enzyme system is a major metabolic pathway for many antidepressant drugs [1], including the serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine [2,3] and duloxetine [3-5]. Ethnic differences in the distribution of CYP isoenzyme polymorphisms have been identified as a source variation in drug metabolism among patient populations [6]. For example, the metabolic activity of CYP2D6, the primary pathway for phase I metabolism for venlafaxine and duloxetine [2,4,5,7], differs for East Asian populations compared with Caucasians; the poor metabolizer CYP2D6 phenotype is rare in Asians, occurring in 2% or less of individuals of Asian descent (Chinese, Japanese and Korean populations) [8,9] compared with approximately 5% to 10% of European and North American Caucasians [8]. Differences in CYP activity can, in turn, give rise to differences in the efficacy or tolerability of drugs that are primarily CYP2D6 substrates [10-12].

Desvenlafaxine (administered as desvenlafaxine succinate), an SNRI approved in the US for the treatment of major depressive disorder (MDD) [13,14], is the major active metabolite of venlafaxine [15]. The free base of desvenlafaxine also is referred to as O-desmethylvenlafaxine (ODV). Desvenlafaxine is primarily excreted unchanged or eliminated via phase II glucuronidation and renal excretion [16]. Desvenlafaxine has minimal interaction with CYP2D6: there was no significant increase in exposure to desipramine and 2-hydroxydesipramine after desvenlafaxine administration [17,18]. Phase I, hepatic metabolism of ODV to N,O-didesmethylvenlafaxine (NODV) via the CYP3A4 pathway appears to play a small role in its elimination [19].

The pharmacokinetic profile of desvenlafaxine has previously been characterized for healthy, predominantly black and white US and

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European subjects [20,21]. Desvenlafaxine has been in development for the MDD indication in Asian countries, including China, Japan, and Korea, and pharmacokinetic studies have been conducted in Japanese and Korean populations [22,23]. Therefore, pharmacokinetic studies of desvenlafaxine in Asian populations are needed. The objectives of the current study were to provide a pharmacokinetic profile, including dose proportionality, and assess the safety and tolerability of single-ascending oral doses of desvenlafaxine in healthy Chinese adults. An additional, aim of the study was to compare the pharmacokinetic profile of desvenlafaxine in healthy Chinese adults with desvenlafaxine pharmacokinetics in other ethnic groups previously studied.

Methods and Materials

The study was a randomized, sponsor-unblinded, single-dose, sequential-group, inpatient study of single-ascending doses of desvenlafaxine in healthy Chinese men and women. It was conducted at 1 investigational site, Shanghai Mental Health Center, Jiao Tong University (Shanghai, China), and the site's institutional review board provided protocol approval and study oversight. Written informed consent was obtained from all subjects before enrollment.

Subjects

Male and nonpregnant/nonlactating female subjects of Chinese descent and living in China were enrolled. Eligible adult subjects (limited to age 18 to 45 years) were healthy, nonsmokers or smokers of less than 10 cigarettes/day, with a body mass index of 19.0 to 24.0 kg/m^2 and body weight of 45 kg or greater. Health status was determined by the investigators based on medical history, physical examination, clinical laboratory test results, vital signs, and 12-lead electrocardiogram (ECG) at screening. Individuals were excluded if they had any significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease; had a history of epilepsy or seizure disorder; or history of drug abuse or alcoholism within 1 year before study day 1; or had positive serologic findings for human immunodeficiency virus antibodies, hepatitis B surface antigen, and/or hepatitis C virus antibodies, or positive findings of urine drug screen. Subjects with any surgical or medical condition that could interfere with the absorption, distribution, metabolism, or excretion of the study drug, or a history of any clinically important drug allergy were also excluded from the trial.

Prohibited treatments

Prohibited treatments included any investigational drugs within 90 days or prescription drugs within 30 days before study day 1; use of any caffeine-containing products, grape juice, grapefruit, grapefruit-containing products, or alcoholic beverages within 48 hours before study day 1; use of any over-the-counter drugs including herbal supplements (except for the occasional use of acetaminophen and vitamins ≤100% recommended daily allowance) within 14 days before study day 1; and donation of blood within 90 days before study day 1.

Study procedures

Each subject participated in the study for approximately 4 weeks. Screening evaluation was carried out within 3 weeks before test article administration, and a 5-day, 4-night inpatient period ran from study day -1 to study day 4. Subjects were randomly assigned to receive a single oral dose of desvenlafaxine 50, 100, and 200 mg or placebo after an overnight fast of at least 10 hours. Randomization was stratified by sex. The placebo group was included in the safety analysis only, to reduce bias based on expected study drug effects. Desvenlafaxine doses were studied sequentially in ascending order. Assessment of the next higher dose was initiated only after the medical monitor determined it was safe to proceed based on safety data from the current dose. At each dose level, 10 subjects were administered desvenlafaxine and 2 received placebo. Plasma samples for pharmacokinetic analysis were collected before (predose), and at 0.5, 1, 2, 3, 4, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, 48, and 72 hours after test article administration. Urine samples were collected before (predose), and at 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72 hours after administration of test article. Samples were frozen and shipped to Cetero Research, Houston, TX, for analysis. Samples were stored at -20°C ± 10°C for up to 34 days (urine) or 42 days (plasma).

Bioanalytical methodology

Plasma samples were assayed for unconjugated ODV, and urine samples were assayed for ODV and NODV by a validated liquid chromatography/tandem mass spectrometry detection (LC/MS/MS) using nadolol (USP; Rockville, MD) as an internal standard. Quantitative determination of ODV in plasma samples and ODV and NODV in urine samples was carried out using an API 3000 LC/MS/MS system (Applied Biosystems, Foster City, CA) equipped with a PE Series 200 LC pump and autosampler, and a Betabasic CN analytical column (100 mm x 2.1 mm, 5 µm equipped with an in-line pre-column filter; Thermo Scientific, Waltham, MA) with a TurboIonspray® interface. Data collection and integration were performed using Applied Biosystems "Analyst" version 1.4.1 software. The slopes, intercepts and correlation coefficients were determined by least-squares linear regression analysis using the ratios of analyte/internal standard peak areas of calibration curve standards in Watson LIMS version 6.4.0.02™ for Windows (Thermo Scientific). The weighting factor of $1/x^2$ ($1/\text{concentration}^2$), which gave the best fit of the data and was the simplest model with the desired performance, was used in the calculation of linear regression line.

Blood sample analysis

For analysis of plasma samples, 9 calibration curve standards (standard concentrations: 2.000, 4.000, 10.00, 20.00, 40.00, 100.0, 200.0, 400.0, and 500.0 ng/mL) and 2 blanks with internal standard and 2 blanks without internal standard were analyzed with each run. The accepted run had an r^2-value of 0.996751 or better for the calibration standard curves. The inter-day precision (% coefficient of variation [%CV]) for the calibration standard was 4.5% or better and the accuracy (% bias) ranged from -2.7% to 2.2%. Two sets of quality control (QC) samples (concentrations: 5.000 ng/mL, 45.00 ng/mL, and 375.0 ng/mL) were assayed with each run. Inter-day precision (%CV) for the quality control samples was 7.4% or better; accuracy (% bias) ranged from -7.0% to -3.5%. The accuracy for the diluted high QC samples was 4.6% and -2.5%, respectively.

Plasma ODV was quantitated using a protein precipitation extraction procedure. A total of 20.0 µL of deionized water was added to each 200 µL aliquot of standard and QC sample, and 20.0 µL of 50% methanol-water solution was added to each 200 µL aliquot of study sample; 0.50 mL of working internal standard solution (50.0 ng/mL) was added to each sample. After vortexing and centrifuging, 200 µL of the supernatant was transferred to an autoinjector vial. Following the addition of 1,000 µL of dilution solution to each vial, 5.00 µL was injected onto the API 3000 LC/MS/MS system. The lower limit of quantitation for unconjugated ODV in plasma samples was 2.000 ng/mL and the upper limit of quantitation was 500.0 ng/mL.

Urine sample analysis

For each urine sample run, 9 calibration curve standards each for

ODV (0.1000, 0.2000, 0.5000, 1.000, 5.000, 10.00, 20.00, 40.00 and 50.00 µg/mL) and NODV (0.04000, 0.08000, 0.2000, 0.4000, 2.000, 4.000, 8.000, 16.00 and 20.00 µg/mL), and 2 blanks with internal standard and 2 blanks without internal standard were analyzed. All accepted runs had r^2-values of 0.997050/0.995893 or better for ODV (total)/ODV (unconjugated) for the ODV calibration standard curves and r^2-values of 0.996966/0.996080 or better for NODV (total)/NODV (unconjugated) for the NODV calibration standard curves. The inter-day precision (% CV) for total ODV was 4.4% or better and the accuracy (%bias) ranged from -2.0% to 2.6%; inter-day precision (% CV) for unconjugated ODV was 7.0% or better and the accuracy (%bias) ranged from -6.2% to 1.8%. For NODV (total), the inter-day precision (% CV) was 5.4% or better and the accuracy (%bias) ranged from -2.3% to 4.4%; inter-day precision (% CV) for unconjugated NODV was 6.1% or better and the accuracy (%bias) ranged from -7.5% to 2.9%. Two sets of QC samples (ODV: 0.3000 µg/mL, 3.000 µg/mL, and 38.00 µg/mL; NODV: 0.1200 µg/mL, 1.200 µg/mL, and 15.20 µg/mL) were assayed with each run. Inter-day precision for the ODV QC samples was 6.2% or better; accuracy ranged from -2.7% to 5.3%. For NODV QC samples, inter-day precision was 6.3% or better and accuracy ranged from -9.7% to 4.2%.

Total ODV and NODV concentrations in urine were quantitated using an enzymatic hydrolysis and dilution extraction procedure. A total of 600 µL of working internal standard solution (500 ng/mL) and 30.0 µL of β-glucuronidase solution were added to each 50.0 µL aliquot of standard, QC and study sample. After incubating for 18 hours at 37°C, the sample was vortexed and centrifuged. Following the transfer of 20.0 µL of the supernatant to an autoinjector vial, 1.30 mL of dilution solution was added and 5.00 µL was injected onto the LC/MS/MS system. Unconjugated ODV and NODV in urine were quantitated using a dilution method, in which each 20.0 µL aliquot of standard, QC sample and study sample was mixed with 0.20 mL of working internal standard solution (500 ng/mL). After vortexing and centrifuging, 20.0 µL of the supernatant was transferred to an autoinjector vial, 1.30 mL of dilution solution was added, and 5.00 µL was injected onto the LC/MS/MS system. The lower and upper limits of quantitation for total and unconjugated ODV in urine samples were 0.1000 µg/mL and 50.00 µg/mL, respectively. For total and unconjugated NODV in urine samples, the limits of quantitation were 0.04000 µg/mL and 20.00 µg/mL, respectively.

Pharmacokinetic analysis

All pharmacokinetic and statistical analyses were performed by the Early Development and Clinical Pharmacology department at Wyeth Research. Plasma and urine concentration-time data were analyzed by the non-compartmental methods of WinNonlin v 5.1.1 software using AutoPilot v 1.2 (Pharsight Corporation, Mountain View, CA). Peak concentration (C_{max}) and time to C_{max} (t_{max}) were read directly from the observed data. Terminal-phase disposition rate constant (λz) for individual concentration-time profiles was determined by the log-linear regression of at least 3 points judged to be in the terminal phase based on individual concentration-time profiles. Terminal-phase elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = \ln 2/\lambda z$.

Total area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) was estimated using the trapezoidal rule during the ascending portion of the curve and the log-trapezoidal rule during the descending portion of the curve. Apparent oral-dose clearance (Cl/F) was estimated as the quotient of dose to the AUC. Apparent volume of distribution for the terminal disposition phase (V_z/F) was calculated as the ratio of Cl/F to λz.

Urine pharmacokinetic parameters included desvenlafaxine amount excreted (Ae) into urine over total collection time, calculated by concentration times urine volume; renal clearance (CL_R), estimated as Ae/AUC; and percentage of excreted unchanged in urine (Ae%; [Ae/Dose]*100).

Statistical analysis

Desvenlafaxine plasma concentrations and pharmacokinetic parameters were summarized by descriptive statistics including %CV, and geometric mean. Preliminary assessments of dose proportionality for fasted C_{max} and AUC were conducted using a power model that measured the degree of nonlinear proportionality:

C_{max} or AUC = a•DOSE^b, where "a" is the coefficient and "b" is the exponent of the regression model.

A lack of fit test was used to determine the validity of the power model for C_{max} and AUC. The model for lack of fit was described by:

log(C_{max}) or log(AUC) = log(DOSE) + LoF, where LoF is a categorical dose-group variable. R^2 was equal to 0.82 and 0.77, respectively, for the linear regression of log(C_{max}) and log(AUC) vs. log(DOSE).

A p-value greater than 0.05 for the lack of fit test indicated that the power model was valid. Effects of desvenlafaxine dose on C_{max} and AUC were also analyzed using analysis of variance. Descriptive statistics were determined for demographic data.

Safety

Safety and tolerability were assessed using adverse event reports, clinical laboratory evaluations (blood chemistry, hematology, and urinalyses), vital signs, and ECGs. Safety assessments were made at baseline, at scheduled intervals post-dose, and at final study evaluation (72 hr post-dose). Adverse events were collected throughout the study period. Treatment-emergent adverse events (TEAEs) were quantified by treatment group and severity. Vital signs, ECGs, and laboratory test results were evaluated for potential clinical importance using predetermined criteria. Adverse events were reported using standard *Medical Dictionary for Regulatory Activities* dictionary terminology.

Results

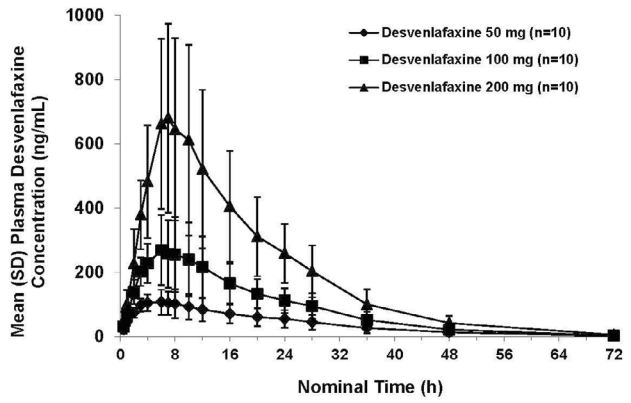
Study population

A total of 36 participants were enrolled (18 male, 18 female), 10 subjects in each desvenlafaxine dose group and 6 in the placebo group (n=2 for each desvenlafaxine dose level). The ratio of males to females was 1:1 at each dose level. All subjects took 1 dose of the test article and were included in the safety population. There were no subject discontinuations; all enrolled subjects completed the study. Demographic and baseline characteristics were similar between treatment groups (Table 1).

Pharmacokinetic analysis

Estimates of plasma pharmacokinetic parameters of desvenlafaxine in healthy Chinese subjects are summarized by treatment group in Table 2. After single dose administration under fasting conditions, desvenlafaxine was absorbed with a median t_{max} of 3.98 to 6.54 hours (range; mean: 4.62 to 6.92 hours) for all doses. Geometric mean $t_{1/2}$ ranged from 8.22 to 9.14 hours. The geometric mean apparent oral clearance was similar across doses (Table 2).

Inter-subject variability (%CV) for C_{max} ranged from 35% to 41%. With a 2-fold increase in dose from 50 to 100 mg, geometric mean



LOQ: Limit of Quantitation; SD: Standard Deviation

Figure 1: Mean (SD) desvenlafaxine plasma concentration-time profiles in healthy Chinese subjects after receiving a single oral dose of 50, 100, or 200 mg desvenlafaxine under fasting conditions.

	Desvenlafaxine 50 mg	Desvenlafaxine 100 mg	Desvenlafaxine 200 mg	Placebo	Total
	(n=10)	(n=10)	(n=10)	(n=6)	(n=36)
Age (yr)					
Mean (SD)	25.5 (1.90)	24.2 (3.05)	25.3 (3.27)	23.2 (1.72)	24.7 (2.69)
Range	23–30	20–28	19–29	20–25	19–30
Sex (n)					
Female	5	5	5	3	18
Male	5	5	5	3	18
Height (cm)					
Mean (SD)	163.9 (8.28)	167.5 (9.51)	164.0 (4.64)	165.0 (5.40)	165.1 (7.28)
Range	152.0–176.0	149.0–178.0	156.0–169.0	159.0–175.0	149.0–178.0
Weight (kg)					
Mean (SD)	58.1 (8.99)	60.3 (9.48)	58.9 (6.11)	56.1 (4.55)	58.6 (7.64)
Range	48.0–72.5	48.0–75.0	51.5–68.0	50.0–62.2	48.0–75.0
BMI (kg/m^2)					
Mean (SD)	21.5 (1.64)	21.4 (1.52)	21.9 (1.41)	20.6 (1.57)	21.4 (1.52)
Range	19.3–23.7	19.5–23.9	19.6–23.8	19.1–22.8	19.1–23.9

BMI: Body Mass Index.

Table 1: Baseline demographic and clinical characteristics of the safety population.

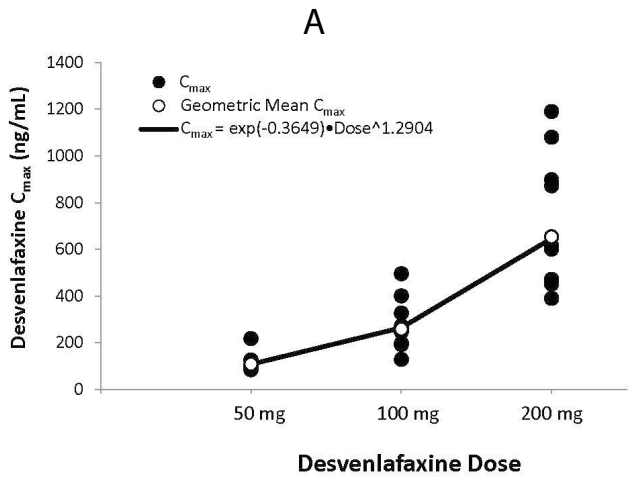
(%CV) C_{max} increased 138%, from 109 (35) ng/mL to 259 (39) ng/mL; C_{max} increased 153% with the dose increase from 100 to 200 mg (654 [41] ng/mL; Figure 1, Figure 2A). Lack of fit tests indicated that the power model was valid for both C_{max} and AUC (P>0.05). In the power model, there was a statistically significant deviation from dose proportionality for C_{max} (b=1.2904, 95% confidence interval [CI]:1.058, 1.523; P<0.05). Dose nonlinearity was described as C_{max} = exp(-0.3649)•Dose^1.2904.

A power model analysis of $AUC_{0-\infty}$ indicated that desvenlafaxine $AUC_{0-\infty}$ increased in a dose-proportional manner (b=1.1728, 95% CI: 0.9281, 1.418), increasing 127% for the dose increase from 50 mg [39] ng•hr/mL) to 100 mg (5,720 [33] ng•hr/mL) and 126% for the increase from 100 to 200 mg (12,900 [35] ng•hr/mL; Figure 2B). Dose linearity was expressed as $AUC_{0-\infty}$ = exp(3.2474)•Dose^1.1728. Inter-subject variability (% CV) for $AUC_{0-\infty}$ ranged from 33% to 39%. No statistically significant effect of desvenlafaxine dose was observed on either C_{max} or $AUC_{0-\infty}$ in this subject population based on the analysis of variance.

Desvenlafaxine Dose	C_{max} (ng/mL)	$t_{1/2}$ (hr)	t_{max} [a] (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Cl/F (L/hr/kg)	V_z/F (L/kg)
50 mg (n=10)	109 (35)	9.14 (18)	3.98 (2.00–8.13)	2520 (39)	0.345 (55)	4.54 (31)
100 mg (n=10)	259 (39)	8.67 (11)	6.05 (2.98–8.03)	5720 (33)	0.294 (18)	3.67 (11)
200 mg (n=10)	654 (41)	8.22 (14)	6.54 (3.98–9.98)	12900 (35)	0.265 (32)	3.15 (20)

$AUC_{0-\infty}$: Area under the Concentration-Time Curve from Time 0 to Infinity.
C_{max}: Peak Plasma Concentration; Cl/F: Clearance; V_z/F: Apparent Volume of Distribution; t_{max}: Time of Peak Concentration; $t_{1/2}$: Mean Terminal Elimination Half-Life.
[a] mean (minimum–maximum).

Table 2: Pharmacokinetic parameters (geometric mean [%CV]) of desvenlafaxine in healthy Chinese subjects receiving a single oral dose of 50, 100, or 200 mg.



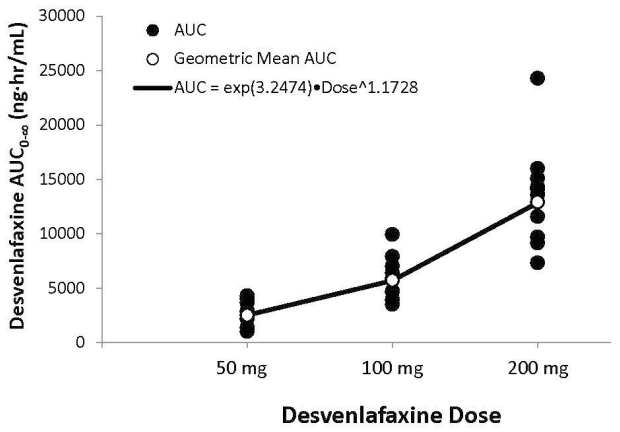
C_{max}: Peak Plasma Concentration

Figure 2A: Relationship between desvenlafaxine C_{max} and dose in healthy Chinese subjects after administration of single oral dose of desvenlafaxine. Model-derived line is shown.

Urinary excretion of total and unconjugated ODV and NODV and CL_R for unconjugated ODV for this sample of healthy Chinese subjects is shown in Table 3. The mean percentage of total desvenlafaxine excreted unchanged in urine was 62.89%, 71.87%, and 88.87% at 50, 100, and 200 mg desvenlafaxine doses, respectively. Excretion of total NODV was minimal, with a mean of 3.92% for the 100 mg dose and 3.64% for the 200 mg dose (not reported for the 50 mg dose). CL_R for unconjugated ODV or desvenlafaxine was approximately 42%, 43% and 56% of total Cl/F at the 50, 100, and 200 mg desvenlafaxine doses, respectively.

Safety/Tolerability

A total of 23/36 (63.9%) subjects reported at least 1 TEAE during the study. TEAEs were reported by 6/10, 8/10, and 8/10 subjects in the 50 mg, 100 mg, and 200 mg desvenlafaxine groups, respectively; 1 of the 6 participants assigned to the placebo group reported TEAEs. Dizziness (14/30 [47%]), nausea (9/30 [30%]), and somnolence (6/30 [20%]) were the most frequently reported TEAEs (reported by greater than 10% desvenlafaxine-treated subjects). The frequencies of dizziness, nausea, and somnolence in the placebo group were 1/6 (16.7%), 1/6 (16.7%), and 0/6, respectively. The TEAEs reported by most subjects (15/23 [65%]) were mild in severity, and none were severe. No serious adverse events or withdrawals because of adverse events were reported.



$AUC_{0-\infty}$: Area under the Concentration-Time Curve to Time Infinity.

Figure 2B: Relationship between desvenlafaxine $AUC_{0-\infty}$ and dose in healthy Chinese subjects after administration of single oral dose of desvenlafaxine. Model-derived line is shown.

	Desvenlafaxine Dose Group		
	50 mg (n=10)	100 mg (n=10)	200 mg (n=10)
	Fraction Excreted (%), Mean (SD)		
Total desvenlafaxine	62.89 (14.91)	71.87 (10.20)	88.87 (8.39)
Unconjugated desvenlafaxine	43.54 (10.73)	46.91 (11.97)	56.01 (14.24)
Total NODV	NR	3.92 (1.22)	3.64 (1.02)
Unconjugated NODV	1.40 (0.69)	1.93 (0.86)	1.61 (0.51)
CL_R, L/hr	9.18 (3.92)	7.86 (1.83)	9.12 (0.53)

CL_R: Renal Clearance for Unconjugated Desvenlafaxine; NODV: N,O-didesmethylvenlafaxine; NR: Not Reported.

Table 3: Urinary excretion of desvenlafaxine and N,O-didesmethylvenlafaxine and CL_R for unconjugated desvenlafaxine.

A total of 9/36 (25%) subjects had at least 1 clinical laboratory result that met a criterion for a potentially clinically important change (1 subject met criteria for >1 result). Potentially clinically important changes included 1 high potassium (placebo) and 2 high phosphorus values (desvenlafaxine 100 mg, 1; placebo, 1), 2 high fasting triglyceride values (desvenlafaxine 100 mg, 1; desvenlafaxine 200 mg, 1), 4 high eosinophils (1 per treatment group), and 1 high platelet count (desvenlafaxine 100 mg). None of those, however, were determined to be clinically important by the medical monitor. Likewise, of the 4/36 (11%) subjects who had vital sign findings that met criteria for potentially clinically important change (3 decreased standing systolic blood pressure [BP; 1 each in desvenlafaxine 50 mg, 100 mg, and 200 mg groups], 1 decreased standing diastolic BP [desvenlafaxine 50 mg], and 1 decreased standing pulse [desvenlafaxine 100 mg]), none were determined to be clinically important. No other observations related to safety were reported or detected in the analysis of this study.

Discussion

This study provides the first available information on the pharmacokinetics and safety of single oral doses of 50, 100, and 200 mg desvenlafaxine in healthy Chinese subjects. Exposure increased in a linearly dose-proportional manner over the dose range studied. There was a statistically significant deviation from dose proportionality for C_{max}; however, AUC increased approximately linearly, 127% and 126% for dose increases from 50 mg to 100 mg and from 100 mg to 200 mg, respectively.

Study	Current Study	Ono et al. 2009 [22]	Nichols et al. 2011 [25]	Nichols et al. 2013 [20]	Baird-Bellaire et al. 2013 [24]
Subjects	Chinese	Japanese	US (6 black, 2 white)	US (13 black, 5 white, 6 other)	Europe
N	10	5	8	24	12
Age, years (mean [SD])	24.2 (3.05)	26.8 (3.6)	52.9 (8.2)	35.0 (8.5)	50.6 (7.0)
Weight, kg (mean [SD])	60.3 (9.48)	58.4 (6.4)	NR	80 (11)	79.1 (18.2)
BMI, kg/m^2 (mean [SD])	21.4 (1.52)	22.6 (2.0)	29.7 (3.9)	NR	26.7 (4.6)
C_{max}, ng/mL (GM [%CV])	259 (39)	238[a] (27)	193.6 (37)	234[b]	176.6 (28)
$AUC_{0-\infty}$, ng × h/ml (GM [%CV])	5,720 (33)	5,646[a] (18)	4,356 (45)	5,376[b]	4,931 (30)
Cl/F, l/h/kg (GM [%CV])	0.294 (18)	0.31[a] (11)	0.288 (64)	0.236[b]	0.263 (18)

$AUC_{0-\infty}$: Area under the Concentration-Time Curve from Time 0 to Infinity; BMI: Body Mass Index; C_{max}: Peak Plasma Concentration; Cl/F: Clearance; GM: Geometric Mean; NR: Not Reported.
[a]Mean (%CV)
[b]%CV not reported

Table 4: Population characteristics and pharmacokinetic parameters for single dose Desvenlafaxine 100 mg.

As expected from desvenlafaxine metabolism, which is largely independent of the CYP pathway [17,18], healthy Chinese subjects exhibited plasma pharmacokinetic profiles similar to those seen in healthy US or European [20,24,25] and Japanese subjects [22]. In this sample of healthy Chinese men and women living in China, geometric mean C_{max}, AUC, and Cl/F were 259 ng/mL, 5,720 ng•hr/mL, and 0.294 L/hr/kg, respectively, for single dose 100 mg desvenlafaxine. For comparison, single dose pharmacokinetics for 100 mg desvenlafaxine have been reported in several studies enrolling healthy US or European subjects (Table 4) [20,24,25]. Mean or geometric mean C_{max} ranged from 176.6 to 234 in US and European subjects (including white, African-American, and "other" race groups) following a single dose of desvenlafaxine 100 mg; AUC ranged from 4,356 to 5,376 ng•hr/mL, and Cl/F ranged from 0.236 to 0.288 L/hr/kg [20,24,25]. However, no direct statistical comparison has been made to test the effect of race on desvenlafaxine pharmacokinetics in those studies. It is also important to note that there were differences other than race/ethnicity between the Asian and US and European subjects enrolled in desvenlafaxine pharmacokinetic studies; Asian subjects were in general younger and had lower mean body weight or BMI compared with US/European subjects (Table 4). Two population pharmacokinetic analyses of desvenlafaxine have been conducted that assessed the effect of race on Cl/F: In one model, developed using sparse pharmacokinetic data obtained from MDD patients combined with rich pharmacokinetic data from healthy subjects, no significant effect of race/ethnicity (white, Arabic, black, Hispanic, Asian, or other) was observed on the Cl/F of desvenlafaxine [26]. In a second model that added pharmacokinetic data from healthy Korean subjects to the first model, geometric mean Cl/F was lower in Korean subjects compared with US subjects [27]. However, Korean subjects had a significantly lower mean body weight compared with US subjects, and there was no meaningful difference between Korean and US healthy subjects for weight-adjusted Cl/F [27].

Safety and tolerability of single-dose desvenlafaxine also appear to be similar in Chinese individuals compared with other populations studied. The most common TEAEs reported by Chinese subjects in this study after administration of single-dose desvenlafaxine 50 mg to 200 mg were dizziness, nausea, and somnolence. Nausea and dizziness were also the most common TEAEs reported by 12 healthy US or European male subjects in a single-ascending-dose pharmacokinetic study who received 150 or 225 mg desvenlafaxine doses [20]. In 24 healthy subjects (54% black, 21% white, 25% other) who received single oral doses of 100 mg, 300 mg, and 600 mg desvenlafaxine, nausea and dizziness were the most common TEAEs reported after administration of each desvenlafaxine dose [20]. The TEAEs reported in this single-dose study of desvenlafaxine are also similar to the adverse events most commonly reported by patients receiving 8-week treatment for MDD [28]. In an integrated analysis of 9 studies of desvenlafaxine (50–400 mg) efficacy and safety for treating MDD, nausea, dry mouth, hyperhidrosis, dizziness and insomnia were reported by 10% or more patients receiving 50 mg/d to 200 mg/d desvenlafaxine (i.e., the doses studied here; n=1,048). In the current study, no severe or serious adverse events were reported, and no clinically important changes in clinical laboratory values, vital signs or ECG recordings were observed.

Limitations

The study had several important limitations. The results were from a sample of healthy adults, and therefore these findings may not generalize to individuals with MDD and who may also have significant medical conditions. The mean age of subjects in this study (24.7 years) was younger than the mean age of patients enrolled in MDD clinical trials (for example, treatment group mean age was 40.7 to 43.7 years in a pooled analysis of 9 desvenlafaxine MDD trials). Also, treatments prohibited in this study included medications and other products that interact with the CYP metabolic pathway and can alter antidepressant pharmacokinetic profiles. Pharmacokinetic profiles may differ in populations using those prohibited treatments, although desvenlafaxine pharmacokinetics are not expected to be affected by inhibitors or substrates of the CYP enzymes. Finally, the pharmacokinetic parameters and urinary excretion results described here are from single doses of desvenlafaxine. Results would be expected to differ following multiple-dose administration of desvenlafaxine.

Conclusions

Single-dose desvenlafaxine was generally well tolerated in this population of healthy Chinese subjects, and its exposure (AUC) over the 50 mg to 200 mg range was dose-proportional. No notable differences in Cl/F were observed between healthy Chinese subjects compared with data from US, European, and Japanese populations in other studies.

Note on Bioanalytical Results

The FDA notified pharmaceutical companies of objectionable conditions at Cetero's Houston, TX, bioanalytical facility following several inspections. Plasma concentration samples for determination of desvenlafaxine were assayed at Cetero during a time period when the FDA is requesting an independent third-party audit to confirm the validity of the data. The independent third-party audit has been conducted as requested by the FDA and has confirmed the acceptability of analytical results for plasma and urine concentrations of desvenlafaxine and NODV obtained from Cetero. Pfizer also conducted a thorough examination and verification of the bioanalytical data generated by Cetero's Houston, TX, bioanalytical facility for this study and has determined that concentration data obtained for this study are accurate.

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Conflicts of interest

Dr. Lingling Guan is an employee of the U.S. Food and Drug Administration (FDA). The research reported in this article was conducted while she was employed at Pfizer (formerly Wyeth Research). The views in this article do not necessarily reflect those of the FDA, and no official support or endorsement of this article by the FDA is intended or should be inferred. Dr. Huafang Li is the PI of the study. Over the past 3 years, she received consulting and educational honoraria from Sanofi-Aventis, AstraZeneca, Johnson & Johnson, Roche, Boehringer Ingelheim, Dainippon Sumitomo, GSK, Servier, Lundbeck, Kingbio, and Jiangsu Hansoh. As the PI, she participated in clinical trials sponsored by Eli Lilly, AstraZeneca, Johnson & Johnson, Roche, Dainippon Sumitomo, GSK, Servier, Lundbeck, Kingbio, and Jiangsu Hansoh.

Dr. Lingling Guan, Zhangjing Chen, Dr. Glen Frick, and Dr. Alice Nichols are former Pfizer Inc. employees.

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