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The Absolute Bioavailability of Desvenlafaxine in Healthy Subjects

Alice I Nichols[1]*, Jessica A Behrle[2], Lyette S Richards[1#], Vernon D Parker[3], Joel A Posener[1#], Richard Fruncillo[1#] and Jeffrey Paul[1#]

[1]*Pfizer Inc, formerly Wyeth Research, Collegeville, Pennsylvania, USA*
[2]*Springhouse, Pennsylvania, USA*
[3]*Orlando, Florida, USA*
[#]*Jessica Behrle, Lyette Richards, Joel Posener, Richard Fruncillo, Jeffrey Paul and Vernon Parker are former employees of Wyeth Research*

Abstract

Background and Objective: Desvenlafaxine (administered as desvenlafaxine succinate) is approved for the treatment of major depressive disorder (MDD). If eliminated by the kidney, desvenlafaxine may have more favorable pharmacokinetic or drug-drug interaction profiles compared to its parent compound, venlafaxine, which depends primarily on the CYP2D6 enzyme system. Therefore, the pharmacokinetics and bioavailability of desvenlafaxine was assessed in healthy human subjects.

Methods: In a single-dose, open-label, crossover study, subjects were randomly assigned to 100 mg/d of oral desvenlafaxine or intravenous (50 mg/1 hr) desvenlafaxine. Plasma and urine were collected for 72 hours post-dosing and assayed to determine pharmacokinetics and bioavailability of (R)-, (S)-, and (R+S)-desvenlafaxine and N,O-didesmethylvenlafaxine.

Results and Discussion: Pharmacokinetic parameters for (R)- and (S)-desvenlafaxine enantiomers were approximately equivalent for the oral and intravenous formulations of desvenlafaxine. Compared with 50 mg intravenous desvenlafaxine, 100 mg oral desvenlafaxine had a higher area under the plasma concentration-time curve and an absolute bioavailability of 80.5%. Urinary excretion of total desvenlafaxine and N,O-didesmethylvenlafaxine accounted for 69% of the orally administered desvenlafaxine dose, with the majority of a dose being excreted unchanged or as the glucuronide conjugate (66%).

Conclusion: Desvenlafaxine has high oral bioavailability and provides an evenly balanced enantiomeric ratio.

Keywords: Desvenlafaxine; Bioavailability; Pharmacokinetics; Intravenous; O-desmethylvenlafaxine; Major depressive disorder

Introduction

Desvenlafaxine is the major active metabolite of venlafaxine [1] and exists as a racemic mixture [2]. It is administered clinically as an orally active succinate salt [3-5]. The free base of desvenlafaxine is also referred to as O-desmethylvenlafaxine (ODV) [3,5]. Desvenlafaxine is approved for the treatment of major depressive disorder (MDD) [3]. Clinical trials have demonstrated its efficacy in the treatment of adults with MDD [6-8].

Like venlafaxine, desvenlafaxine primarily inhibits the reuptake of serotonin and norepinephrine, with little inhibition of dopamine reuptake [4]; however, these agents differ in their metabolic profiles. The biotransformation of venlafaxine to desvenlafaxine is primarily dependent on the CYP2D6 enzyme system [9,10]. Due to the polymorphic nature of CYP2D6 gene loci and resultant array of metabolizer phenotypes, the extent of this conversion can vary across a patient population. In addition, conversion of venlafaxine to desvenlafaxine can be affected by drug-drug interactions with medications that inhibit CYP2D6 – a particular concern in depressed patients, who are often taking a number of different medications [11].

In vitro studies of desvenlafaxine using human liver microsomes indicate that it is metabolized primarily to N,O-didesmethylvenlafaxine and M9, a metabolite hydroxylated on the benzyl group; further in vitro observations indicate that this metabolism is not dependent on CYP2D6 [12]. Animal studies indicate that desvenlafaxine is mainly eliminated via renal excretion of the unchanged drug or its glucuronide conjugate, suggesting overall limited hepatic involvement in desvenlafaxine elimination [12]. It was thus speculated that desvenlafaxine elimination in humans may also occur primarily at the level of the kidney, which might translate to a more favorable pharmacokinetic or drug-drug interaction profile compared to its parent compound venlafaxine.

Formal statistical testing has shown that desvenlafaxine pharmacokinetics is linear and dose proportional over a single-dose range of 100 to 600 mg [13], further investigation supports proportional decreases in exposure for doses of 25 and 50 mg in relation to a dose of 100 mg (data on file). In addition, multiple-dose accumulation of desvenlafaxine is predictable from the single-dose pharmacokinetic profile [14]. The objective of this investigation was to determine the absolute bioavailability and pharmacokinetic characteristics of single, oral doses of desvenlafaxine (100 mg) in healthy adults.

Methods

Subjects

Males and females 18 to 45 years of age, found to be healthy based on history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory test results at screening, were eligible to

***Corresponding author:** Alice I. Nichols, Pfizer Inc, formerly Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA, Tel: 484-865-8741; Fax: 484-865-9075; E-mail: alice.nichols@pfizer.com

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participate. Exclusion criteria included the presence or history of any significant disease or any disorder that may prevent successful completion of the study, and alcohol and/or drug abuse. All potential subjects provided written informed consent in compliance with the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines and in accordance with the Declaration of Helsinki and the United States Food and Drug Administration regulations. Independent Ethics Committee/Institutional Review Board approval of each protocol was obtained.

Concomitant therapies

No concomitant therapies were permitted; women of childbearing potential were required to use an acceptable method of birth control other than oral contraceptives or hormonally treated intrauterine devices.

Study design and overview

This was an open-label, randomized, 2-period, inpatient study conducted at a single investigation site to assess the absolute bioavailability and pharmacokinetic profile of desvenlafaxine in healthy subjects. Treatments consisted of a single, oral, 100-mg dose of desvenlafaxine and a single, intravenous (IV) dose of 50-mg desvenlafaxine infused over 1 hour. Subjects were randomly assigned to receive one of the formulations in the first period and the other formulation in the second period. Subjects participated in the study for 29 days, including a screening evaluation within 3 weeks before study day 1 and a 9-day, 8-night inpatient period (beginning on day –1).

Study procedures

On day –1, eligible subjects reported to the study site; eligibility was reviewed and brief assessments were carried out. Those subjects remaining eligible to participate were confined to the study clinic for 9 days and 8 nights. A medical history was obtained at screening, and physical examinations were performed at screening, on study day –1, and at the final study evaluation. On study day 1, after an overnight fast of ≥10 hours, predose assessments were conducted; at approximately 0800 hours the assigned study drug was administered. Oral desvenlafaxine 100 mg was given with 240 mL room temperature water. All subjects received the study drug in an upright position and remained in a semirecumbent position for 2 hours after study drug administration. Blood and urine samples were collected for up to 72 hours postdosing. The washout between study drug administration periods was ≥96 hours, and the second administration of assigned study drug (ie, either oral or IV dose of desvenlafaxine) was given on study day 5. Adverse events (AEs) were continuously monitored throughout the study. The investigator determined whether it was safe to discharge each subject from the study site based on review of clinical status.

Blood sample collection

Venous blood samples (10 mL) were collected in evacuated, heparinized tubes. For subjects given 100-mg oral desvenlafaxine, samples were obtained at 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dose administration. For subjects given IV desvenlafaxine (50 mg over 1 hour), samples were obtained at 0, 0.5, 1, 1.25, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dose administration.

Urine sample collection

Urine was collected during the following intervals: –2 to 0 hours (predesvenlafaxine), 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 48 hours, and 48 to 72 hours after dose administration. Aliquots (20 mL) of urine were retained from each collection period for assay of desvenlafaxine and metabolites. At 24 hours postdosing, all urine collected was pooled and a 20 mL aliquot was retained for creatinine determination.

Bioanalytical Methodology

Desvenlafaxine enantiomeric ratios in plasma

To determine the enantiomeric ratio (S) - to (R) - desvenlafaxine in the study samples, a validated turbo ion spray, chiral column chromatography/tandem mass spectrometry (LC/MS/MS) method was performed by Advion Biosciences (Ithaca, NY). The LC/MS/MS system consisted of two LC-10AD pumps, an SCL-10A pump controller, a PE200 autosampler, an Astec Chirobiotic V® column (4.6 mm X 100 mm) and a SCIEX API 3000 mass spectrometer (Applied Biosystems, Concord, Ontario).

Calibration curve samples were prepared at desvenlafaxine concentrations of 5, 10, 25, 50, 100, 250, 375, 500, and 700 ng/mL. This is a nonquantitative assay in which the (S) to (R) ratio is determined over a specified concentration range; as such, calibration standards were used only to demonstrate the accuracy of this measurement. Human plasma quality control (QC) samples were prepared at desvenlafaxine concentrations of 15, 125, and 400 ng/mL at (S) - to (R)-enantiomeric ratios of 20:80 and 80:20.

Plasma samples (0.25 mL) were prepared using a solid-phase extraction (SPE) procedure. Samples (250 µL) and QC samples were aliquoted into tomtec tubes. The Isolute C_8 (100 mg) SPE extraction block was conditioned with 1.0 mL of methanol, then equilibrated with 1.0 mL of water. Samples were mixed, loaded into the SPE block, and aspirated through the cartridge at 1 mL/min. The SPE block was washed with 1.0 mL water, then with 1.0 mL 50:50 methanol: water and a full vacuum was applied. A 96-well collection block was placed into the vacuum manifold, the analytes were eluted off the block with 0.5 mL of methanol; a full vacuum was applied and the collection block removed. The eluate was evaporated to dryness under nitrogen at 35°C; extracts were reconstituted in 150 µL of 25:75 isopropanol: 10 mM ammonium acetate, pH 4.2, vortexed, and centrifuged. 10 µL – 20 µL were injected onto the HPLC column. The flow rate was 1 mL/minute and the autosampler run time was 8.2 minutes. The typical retention time was 5.5 minutes (±1 minute) for the S- enantiomer and 6.5 minutes (±1 minute) for the R- enantiomer. For the mass spectrometry, positive ions were measured in selected reaction monitoring mode; ion masses monitored were 264.2-201.1.

Peak areas were integrated by the SCIEX program MacQuan, version 1.6, residing on a Macintosh computer. Following peak area integration, the results tables from MacQuan were saved as text files and then transferred to Excel for calculations and data table preparation. All calculations to determine enantiomeric ratios were based on the peak area of S- or R-desvenlafaxine to the total area of both enantiomers. For the QC samples, the interassay and intraassay accuracy ranged from -14.5% to 13.5%, and the precision ranged from 0.0453 to 11.1%. For the calibration standards, the interassay accuracy of the (S) - to (R)-desvenlafaxine ratios was within ±2.86%, and the precision ranged from 3.57% to 14.1%.

Desvenlafaxine concentration in plasma

To determine the plasma concentrations of desvenlafaxine in the study samples, a high-performance, liquid chromatography method

with fluorescence detection was performed by Bioassay Laboratories (Houston, TX), using propranolol hydrochloride as an internal standard. The HPLC system was equipped with a pump (Shimadzu LC-9A), an autosampler (Waters 717), a fluorescence detector (Shimadzu RF-535), and an analytical column (Spherisorb CN, 25 cm x 4.6 mm, 5 micron, with an in-line, precolumn filter).

Eight different standard concentrations were used for the calibration curve. A single calibration curve was analyzed with each batch run. The curve for all accepted runs had "r" values of 0.996253 or better. Quality control samples were prepared at concentrations of 15.0 ng/mL, 60.0 ng/mL, and 300.0 ng/mL; two sets of QC samples were assayed with each run.

Desvenlafaxine was quantitated using a liquid-liquid extraction procedure. To each 1.0 mL aliquot of plasma sample, 0.6 mL working internal standard solution (1000 ng/mL) and 0.2 mL of saturated sodium borate solution was added. After vortexing, the sample was extracted with 6.0 mL of ethyl ether; the ether layer was separated and extracted with 0.3 mL of 0.01N hydrochloric acid solution; the upper organic layer was discarded and residual ether evaporated. To the acid layer, 50.0 µL of mobile phase was added; a 50.0 µL aliquot was injected onto the HPLC system. The flow rate was 1.1 mL/min (±20%), and autosampler run time was 25 minutes. The retention time for desvenlafaxine was 12.7 minutes (±20%). The fluorescent wavelengths used were EX 230 nm and EM 300 nm.

Data were collected and calculated on a Waters Millennium[32] Chromatography Manager Software System, version 4.00. Linear regression, with 1/x weighting, was used to obtain the best fit of data for the calibration curves. The minimum quantifiable concentration for (R)-, (S)-, and (R+S)-desvenlafaxine was 5.0 ng/mL plasma, and the upper limit of quantitation was 500 ng/mL. For the QC standards, the interday accuracy ranged from 92.9850 to 102.9473%, and the interday precision was 9.9222% or better. For the calibration standards, the interday accuracy ranged from 94.0793 to 106.1050%, and the interday precision was 5.7373% or better.

Desvenlafaxine and NODV concentration in urine

To determine the concentration of unconjugated and total (unconjugated plus conjugated) desvenlafaxine and NODV, a method employing a validated high performance liquid chromatography with UV detection was performed by Bioassay Laboratories using 2-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl)-phenol hydrochloride as an internal standard. The HPLC system was equipped with a pump (Shimadzu LC-9A), an autosampler (Waters 717), a UV detector (Spectro Monitor 3200), and an analytical column (Supelco Supelcosil LC-8-DB, 15 cm x 4.6 mm, 5 micron, equipped with an in-line, precolumn filter).

Seven different standard concentrations of desvenlafaxine/NODV were used for the calibration curve. A single calibration curve was analyzed with each batch run. For total desvenlafaxine and NODV, respectively, the curve for all accepted runs had "r" values of 0.998920 and 0.998234 or better. For unconjugated desvenlafaxine and NODV, respectively, the curve for all accepted runs had "r" values of 0.998926 and 0.999313 or better. Quality control samples were prepared at concentrations of 0.25/0.25 µg/mL, 1.5/1.5 µg/mL, and 8.0/8.0 µg/mL for desvenlafaxine and NODV; two sets of QC samples were assayed with each run.

Desvenlafaxine and NODV were quantitated using a liquid-liquid extraction procedure. For total desvenlafaxine/NODV, to each 0.10 mL aliquot of urine sample, 1.0 mL of working internal standard solution (1500 ng/mL) and 30.0 µL of ß-glucuronidase (7500 units/mL) were added and the tubes were incubated at 37°C for 18 hours. For unconjugated desvenlafaxine, to each 0.1 mL aliquot of study sample, 1.0 mL working internal standard solution (800 ng/mL) was added. The procedure from this step forward was the same for total and unconjugated analytes: 0.2 mL of saturated sodium tetraborate solution was added, the samples were vortexed, and 5.0 mL of ethyl ether was added. The samples were shaken and centrifuged; the organic layer was transferred and 0.30 mL of 0.01N hydrochloric acid solution was added; the samples were shaken and centrifuged, the organic layer was discarded and residual ether evaporated. To the acid layer, 50.0 µL of mobile phase were added; a 50.0 µL aliquot was injected onto the HPLC system. The flow rate was 0.8 mL/min (±20%), and autosampler run time was 32 minutes. Retention times for desvenlafaxine and NODV were 8.42 minutes (±20%) and 7.48 minutes (±20%), respectively. The wavelength used was 229 nm.

Data were collected and integrated (height mode) by a Millennium[32] Chromatography Manager Software System, version 4.00. The weight factor of 1/y (ie, 1/ratio) was used in the calculation of the linear regression line. The minimum quantifiable concentration for desvenlafaxine and NODV was 0.1 µg/mL, and the upper limit of quantitation was 10.0 µg/mL.

For the total desvenlafaxine QC standards, the interday accuracy ranged from 99.0688 to 101.2000%, and the interday precision was 4.1897% or better. For the total NODV QC standards, the interday accuracy ranged from 99.5800 to 103.2575%, and the interday precision was 8.6957% or better. For the total desvenlafaxine calibration standards, the interday accuracy ranged from 96.1000 to 105.0000%, and the interday precision was 6.0952% or better. For the total NODV calibration standards, the interday accuracy ranged from 94.7900 to 108.5000%, and the interday precision was 8.2949% or better.

For the unconjugated desvenlafaxine QC standards, the interday accuracy ranged from 100.4338 to 102.2400%, and the interday precision was 6.9249% or better. For the unconjugated NODV QC standards, the interday accuracy ranged from 103.3463 to 105.1200%, and the interday precision was 5.2143% or better. For the unconjugated desvenlafaxine calibration standards, the interday accuracy ranged from 96.0400 to 103.4000%, and the interday precision was 6.2476% or better. For the unconjugated NODV calibration standards, the interday accuracy ranged from 95.4400 to 111.8000%, and the interday precision was 5.7245% or better.

Statistical Analysis

Plasma concentrations of (R) - and (S)-enantiomers of desvenlafaxine were determined as the product of each enantiomer fraction of racemic mixture and the concentration of racemic desvenlafaxine. Plasma (R)-, (S)-, and racemic desvenlafaxine peak plasma concentration (C_{max}) and time to C_{max} were taken directly from the observed data; model-independent methods were used to analyze other plasma pharmacokinetic parameters including area under the concentration-time curve (AUC), terminal-phase elimination half-life ($t_{1/2}$), apparent volume of distribution after oral administration based on the terminal phase (V_z/F); and apparent volume distribution after IV administration ($V_z=CL/\lambda_z$). The terminal-phase elimination rate constant (λ_z) was estimated using a log-linear regression of the last 3 or more plasma concentrations that were determined to be in the log-linear elimination

phase by visual inspection. The $t_{1/2}$ was calculated as $t_{1/2}=0.693/\lambda_z$. The total AUC was defined as $AUC_T + CT/\lambda_z$, where AUC_T is the area under the single-dose plasma concentration-time curve (AUC_T) truncated at the last observed plasma concentration (CT) at time T and calculated by using the log-trapezoidal rule for decreasing concentrations and the linear-trapezoidal rule for increasing concentrations. Cl/F was calculated as dose/AUC, and V_z/F was calculated as $Cl/F/\lambda_z$. IV clearance (Cl) was calculated as the IV dose divided by the AUC after IV administration. Absolute oral bioavailability of (R)-, (S)-, and racemic desvenlafaxine was estimated for each subject by calculating the ratio of oral to IV AUC (AUC_{oral}/AUC_{IV} with dose normalization). Urine amounts of total (conjugated and unconjugated) and unconjugated desvenlafaxine and total and unconjugated NODV were reported for each collection interval as well as for the entire 0- to 72-hour postdose study period. Other urinary excretion measures that were calculated included percentage of dose recovered in urine, total urinary recovery of desvenlafaxine and its metabolites, desvenlafaxine renal clearance (CL_R), and percent IV clearance. CL_R was calculated as the total amount of unconjugated desvenlafaxine excreted in urine divided by the plasma AUC of desvenlafaxine. Percent IV clearance accounted for by renal elimination of unconjugated desvenlafaxine was calculated as CL_R divided by Cl.

Summary descriptive statistics including mean, median, standard deviation, and range were obtained for all demographic data, vital signs, ECG parameters, laboratory parameters, plasma concentrations, and urine concentrations. Mean changes from baseline in vital signs, clinical laboratory test results, physical examinations, and ECG parameters were examined for potential clinical significance based on predefined criteria. Estimates of pharmacokinetic parameters were determined for the relevant treatment groups. Formal statistical comparisons between the oral and IV desvenlafaxine dosage forms were not performed.

Results

Subjects

Fourteen subjects were enrolled in and completed the study. Table 1 summarizes demographic and baseline characteristics of the study.

Plasma pharmacokinetics of desvenlafaxine

For each formulation of desvenlafaxine, plasma concentrations of the (R) - and (S)-desvenlafaxine enantiomers were comparable, resulting in closely similar pharmacokinetic parameters obtained for each enantiomer. Desvenlafaxine plasma concentrations peaked at the end of the 1-hour 50 mg IV desvenlafaxine infusion and about 6 hours after administration of 100-mg oral desvenlafaxine (Figure 1). C_{max} was approximately 45% higher after IV than after oral administration of desvenlafaxine. Clearance following IV administration was 0.26 L/h/kg for racemic desvenlafaxine. Desvenlafaxine $t_{1/2}$ was comparable after both oral and IV administration (Table 2). With oral desvenlafaxine, geometric mean AUC was higher compared with IV desvenlafaxine (3728 vs 2366 ng*h/mL, respectively). Mean absolute desvenlafaxine bioavailability, based on dose-normalized comparison of AUC values, was 80.5% with oral versus IV desvenlafaxine.

Urinary excretion parameters

Table 3 summarizes the urinary recovery of unconjugated and conjugated (R+S)-desvenlafaxine and unconjugated and conjugated NODV during 72 hours postdosing. Urinary excretion of conjugated and unconjugated desvenlafaxine and NODV accounted for the majority of the administered dose of desvenlafaxine (oral: 69%, IV: 76%; Table 3). The proportion of unconjugated and conjugated desvenlafaxine recovered from urine was comparable regardless of route of administration. Similarly, the proportion of dose excreted as NODV also was comparable with oral and IV routes of administration. The geometric mean CL_R of unconjugated desvenlafaxine was similar regardless of oral versus IV desvenlafaxine administration (222 mL/min and 202 mL/min, respectively).

Characteristic	(N=14)
Age (years), Mean (SD)	29.6 (6.8)
Sex, n (%)	
Female	0
Male	14 (100)
Race, n (%)	
Black	7 (50)
Other	3 (21)
White	4 (29)
Height (cm), Mean (SD)	182.3 (5.9)
Weight (kg), Mean (SD)	81.7 (9.7)
BMI (kg/m^2), Mean (SD)	24.6 (2.8)

Abbreviations: BMI- Body Mass Index; SD- Standard Deviation.

Table 1: Demographic and Baseline Characteristics of Subjects.

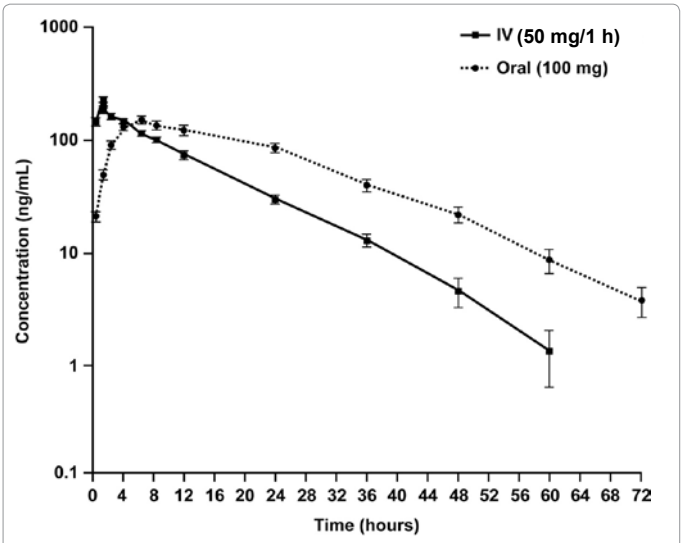

Figure 1: Plasma Concentration Over Time Profile for Racemic (R+S) Desvenlafaxine, After Administration of Oral Desvenlafaxine 100 mg or IV Desvenlafaxine 50 mg/1 h (N=14).

Discussion

This investigation characterized the absolute bioavailability of a single, oral dose of desvenlafaxine 100 mg as well as the pharmacokinetic characteristics of a single dose of either oral (100 mg) or IV (50 mg, 1 hour administration) desvenlafaxine in healthy adults. The pharmacokinetic profiles observed indicate that desvenlafaxine exhibits a high level of systemic absorption after oral administration. The absolute bioavailability with 100-mg oral desvenlafaxine, relative to IV desvenlafaxine (50 mg infused over 1 hour), was 80.5%, which is substantially greater than the reported absolute bioavailability of desvenlafaxine's parent compound venlafaxine (44% and 40% for the

Enantiomer/ Treatment	Variables	C_{max}, (ng/mL)	t_{max}, (h)	$t_{1/2}$ (h)	AUC (ng*h/mL)	Cl /F (L/h/kg)	V_z (L/kg)	AUC_{oral}/AUC_{IV}
(R)-enantiomer desvenlafaxine								
IV desvenlafaxine 50 mg/1 h	Mean (SD) %CV Geo. Mean Min-Max	111.5 (25.5) 23% 108.8 78.4–156.1	1.0 (0.03) 3% 1.0 1.0–1.1	9.9 (3.1) 31% 9.5 6.2–17.7	1173 (291) 25% 1134 577–1590	0.280 (0.076) 27% 0.272 0.192–0.450	3.857 (1.058) 27.4% 3.736 2.055–6.772	
Oral desvenlafaxine 100 mg	Mean (SD) %CV Geo. Mean Min-Max	76.7 (20.0) 26% 74.2 41.8–115.1	7.0 (2.6) 37% 6.6 4.0–12.0	10.3 (1.9) 19% 10.1 6.7–14.0	1915 (615) 32% 1785 481–2828			0.804 (0.155) 19.3% 0.787 0.417–1.053
(S)-enantiomer desvenlafaxine								
IV desvenlafaxine 50 mg/1 h	Mean (SD) %CV Geo. Mean Min-Max	120.2 (27.6) 23% 117.3 85.0–176.0	1.0 (0.03) 3% 1.0 1.0–1.1	9.5 (2.0) 21% 9.3 6.4–12.2	1262 (299) 24% 1224 652–1634	0.259 (0.065) 25% 0.252 0.185–0.398	3.397 (0.504) 14.8% 3.362 2.441–4.295	
Oral desvenlafaxine 100 mg	Mean (SD) %CV Geo. Mean Min-Max	83.1 (22.3) 27% 80.2 47.7–128.2	6.6 (2.1) 33% 6.3 4 .0–12.0	10.2 (2.0) 20% 10.0 6.9–14.5	2057 (643) 31% 1925 542–3017			0.804 (0.155) 19.3% 0.787 0.416–1.050
Racemic (R+S) desvenlafaxine								
IV desvenlafaxine 50 mg/1 h	Mean (SD) %CV Geo. Mean Min-Max	231.6 (53.0) 23% 226.2 163.4–332.1	1.0 (0.03) 3% 1.0 1.0–1.1	9.8 (2.1) 21% 9.6 7.3–13.9	2442 (585) 24% 2366 1233–3261	0.268 (0.068) 26% 0.260 0.188–0.420	3.664 (0.546) 14.9% 3.624 2.529–4.468	
Oral desvenlafaxine 100 mg	Mean (SD) %CV Geo. Mean Min-Max	159.6 (42.2) 27% 154.3 89.4–243.3	6.4 (2.1) 33% 6.1 4.0–12.0	10.4 (2.0) 19% 10.2 6.9–14.3	3993 (1271) 32% 3728 1023–5844			0.805 (0.157) 19.6% 0.788 0.415–1.059

Abbreviations: AUC: Area Under the Plasma Concentration-time curve; Cl/F: Apparent Oral-dose Clearance (dose/AUC); C_{max}: Peak Plasma Concentration; CV: Coefficient of Variation; Geo. Mean: Geometric Mean; IV: Intravenous; Max: Maximum; Min: Minimum; SD: Standard Deviation; $t_{1/2}$: Terminal-phase Elimination Half-life; t_{max}: Time to peak concentration; Vz: Apparent volume of distribution after administration based on the terminal phase

Table 2: Summary of Plasma Desvenlafaxine Pharmacokinetic Parameters.

		Unconjugated (% dose)			Total unconjugated and conjugated (% dose)		
Treatment Group	Variables	(R+S)-Desvenlafaxine	NODV	CL_R mL/min	(R+S)-Desvenlafaxine	NODV	Sum Total (R+S)-Desvenlafaxine and NODV
IV desvenlafaxine 50 mg/h	Mean (SD) %CV Geo. Mean Min-Max	51.5 (11.4) 22% 50.0 22.0-63.8	1.6 (1.1) 67% 1.1 0.1-3.5	202 ± 96 47% 185 85-468	72.3 (14.5) 20% 70.5 32.6-88.7	3.6 (1.2) 34% 3.3 1.0-5.2	75.9 (15.1) 20% 74.0 33.6-93.8
Oral desvenlafaxine 100 mg	Mean (SD) %CV Geo. Mean Min-Max	46.4 (9.9) 21% 45.3 24.5-64.6	1.9 (1.0) 55% 1.5 0.2-3.9	222 ± 82 37% 211 145-454	65.5 (10.8) 17% 64.5 39.4-76.3	3.5 (1.3) 38% 3.3 1.4-6.6	69.0 (11.8) 17% 67.9 40.9-82.9

Abbreviations: % dose: Percent of the dose of study drug given, which is a combination of both (R)- and (S)-enantiomers; CL_R: Renal clearance; CV: Coefficient of Variation; Geo. Mean: Geometric Mean; IV: Intravenous; Max: Maximum; Min: Minimum; NODV: N,O-didesmethylvenlafaxine; SD: Standard Deviation

Table 3: Urinary Recovery of Unconjugated and Conjugated (R+S)-Desvenlafaxine and Unconjugated and Conjugated NODV.

conventional and extended-release formulations, respectively) [15]. Approximately equal concentrations of the (R) - and (S)-enantiomers of desvenlafaxine were obtained from all plasma samples assayed; therefore, pharmacokinetic parameters for each enantiomer were comparable. Moreover, urinary excretion analyses showed that the percentage of the given doses recovered in urine as unconjugated or conjugated desvenlafaxine and NODV were 69% with 100-mg oral desvenlafaxine and 76% with IV 50-mg desvenlafaxine. The elimination of desvenlafaxine is largely dependent on urinary excretion, because the majority of the administered dose was excreted in the urine as unchanged desvenlafaxine (46%) or its glucuronide conjugate (19%), with less than 5% excreted as NODV or NODV glucoronide. Overall, these findings indicate that desvenlafaxine has a simple, limited metabolism.

Limitations

The pharmacokinetic parameters described here are based on single doses of desvenlafaxine in healthy adults between the ages of 18

and 45 years; pharmacokinetic results could be altered in younger or older individuals or those with significant medical conditions.

Conclusions

The present findings indicate that in healthy adults a single, oral dose of desvenlafaxine 100 mg is well absorbed, with the majority of a dose being excreted unchanged or as the glucuronide conjugate in the urine. A single dose of either oral (100 mg) or IV (50 mg) desvenlafaxine yields approximately equivalent exposure to the (R) - and (S)-desvenlafaxine enantiomers.

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Disclosure

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