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Pharmacokinetics, Pharmacodynamics, and Safety of Desvenlafaxine, a Serotonin-Norepinephrine Reuptake Inhibitor

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Abstract

Study background: Assess safety, tolerability, pharmacokinetics, and pharmacodynamics of desvenlafaxine (administered as desvenlafaxine succinate) in 3 studies with healthy volunteers.

Methods: Study 1, a randomized, open-label, dose proportionality, crossover study, assessed pharmacokinetics and safety of single doses of desvenlafaxine 100, 300, and 600 mg (N=24). Study 2, a randomized, double-blind, placebo-controlled, sequential-group, single-ascending dose study, assessed pharmacokinetics, pharmacodynamics, and safety of desvenlafaxine 150–900 mg and venlafaxine extended-release 150 mg (N=79). Study 3, a double-blind, placebo-controlled, sequential-group, multiple-ascending dose study, assessed pharmacokinetics, pharmacodynamics, and safety of desvenlafaxine 300, 450, and 600 mg (N=36). In all studies, safety was monitored through adverse events, physical examinations, electrocardiograms, laboratory tests, and vital signs. In study 2, a daytime spectral analysis of electroencephalogram data was conducted; in studies 2 and 3, cognition was assessed using vigilance and psychomotor performance tests.

Results: Following single- and multiple-dose administration, desvenlafaxine C_{max} and AUC increased in linear, dose-proportional manner over doses of 100–900 mg. Steady-state plasma concentrations were reached within 4–5 days, and multiple-dose pharmacokinetics were adequately predicted from single-dose pharmacokinetics. The maximum tolerated single dose was 750 mg; vomiting was the dose-limiting adverse event. For multiple doses, the maximum tolerated dose was 450 mg/d; orthostatic hypotension was dose-limiting. Adverse events at doses below the maximum tolerated doses were generally mild and transient. Absolute beta energies significantly increased in all electroencephalogram leads with doses ≥ 450 mg, particularly in front temporal lobes. Single or multiple desvenlafaxine doses did not alter psychomotor function or memory.

Conclusion: Maximum tolerated doses for desvenlafaxine (750 mg, single dose; 450 mg, multiple doses) were well above the recommended therapeutic dose of 50 mg/d for major depressive disorder. Desvenlafaxine exhibited approximately linear, dose-proportional pharmacokinetics across the wide range of doses studied and was not associated with significant alterations in psychomotor function or memory.

Keywords: Desvenlafaxine; Pharmacokinetics; Pharmacodynamics; Tolerability; Maximum tolerated dose; Dose proportionality

Abbreviations: AEs: Adverse Events; AUC: Area Under the Plasma Concentration-Time Curve; AUCss: Area Under the steady-state Plasma Concentration-Time Curve; CRT: Choice Reaction Time; C_{max}: Peak Drug Concentration; DSST: Digit Symbol Substitutions Test; EEG: Electroencephalogram; ECG: Electrocardiogram; ER: Extended Release; HPLC: High Performance Liquid Chromatography; MDD: Major Depressive Disorder; MTD: Maximum Tolerated Dose; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; TEAE: Treatment-Emergent Adverse Event; ODV: O-Desmethyl Venlafaxine; T_{max}: Time of Peak Concentration; VAS: Visual Analog Scale; V_z/F: Volume of Distribution

Introduction

Desvenlafaxine (administered as desvenlafaxine succinate) is the major active metabolite of the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine; the free base of desvenlafaxine also is referred to as O-desmethylvenlafaxine (ODV) [1,2]. Desvenlafaxine, administered clinically as a succinate salt, is approved for the treatment of major depressive disorder (MDD).

Like venlafaxine, desvenlafaxine is chemically unrelated to tricyclic agents or selective serotonin reuptake inhibitors. It is classified as an SNRI and has been shown to inhibit the neuronal reuptake of serotonin and norepinephrine, with little inhibition of dopamine reuptake. Desvenlafaxine does not possess monoamine oxidase inhibitory activity, nor does it have any significant affinity for muscarinic, cholinergic, H_1-histaminergic, or α_1-adrenergic receptors, which can cause dry mouth, constipation, urinary retention, visual disturbances, or sedation [1-3].

The preclinical pharmacologic profile of desvenlafaxine is suggestive of activity in various central nervous system-related disorders associated with the norepinephrine and serotonin systems [3]. Data from published studies have confirmed the efficacy, safety, and tolerability of desvenlafaxine in the treatment of MDD [4,5].

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This report presents the results of 3 separate studies designed to characterize the safety and tolerability, pharmacokinetic properties, and dose proportionality of desvenlafaxine in human subjects. The studies enrolled healthy subjects who received single or multiple doses of desvenlafaxine.

Materials and Methods

Subjects

Eligible participants were required to have a normal physical exam, clinical laboratory evaluation, and 12-lead electrocardiogram (ECG). Subjects were ineligible if they had significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, or central nervous system diseases or a surgical or medical condition that could interfere with the absorption, distribution, metabolism, or excretion of desvenlafaxine. Investigational or prescription drugs, including oral contraceptives and hormonal therapies, were not allowed within 90 days of the start of the study. Over-the-counter drugs were not allowed within 14 days. All studies received approval from a local, independent ethics committee or an institutional review board and written informed consent was obtained from all subjects prior to the studies.

Study design

Study 1 (MDS Pharma Services; Neptune, NJ) was a dose-proportionality study that used a randomized, open-label, inpatient, 3-treatment, crossover design and enrolled 24 healthy subjects to receive at least 1 dose of desvenlafaxine. The safety and tolerability of desvenlafaxine following single-dose oral administration also were evaluated. Patients received single doses of desvenlafaxine 100, 300, and 600 mg during 3 separate 4-day study periods; the sequence of dose level administration for each patient was determined using a randomization schedule. On the morning of the first day of each study period, subjects received 1 of the 3 doses of desvenlafaxine (100, 300, or 600 mg) up to 30 minutes after a medium-fat breakfast. Blood samples were then collected at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours for pharmacokinetic analysis. Following a 24-hour washout period after final blood samples were collected at one dose level, a single dose of desvenlafaxine (at the next dose level) was administered, and blood sampling recommenced. The final evaluation was performed 72 hours after final test article administration for all subjects, or at the time of early withdrawal, as applicable.

Study 2 (Parexel-Cemaf; Poitiers, France) was a randomized, double-blind, placebo-controlled, sequential-group, single-ascending-dose study that was primarily conducted to evaluate the safety and tolerability of single doses of desvenlafaxine. Secondarily, the pharmacokinetics and pharmacodynamics of desvenlafaxine were also evaluated. A total of 79 male subjects were randomly assigned to receive desvenlafaxine 150, 225, 300, 450, 600, 750, and 900 mg; venlafaxine extended release (ER) 150 mg; or placebo. Each subject participated in only 1 dose group. Desvenlafaxine was administered 1 dose at a time, and the safety and tolerability of the preceding dose needed to be confirmed before the next higher dose was administered. Subjects received a medium-fat breakfast on the morning of day 1 that was to be completely consumed within approximately 10 minutes prior to test article administration. Subjects were then administered a single dose of desvenlafaxine, venlafaxine ER, or placebo, and timed blood samples were collected over the subsequent 72-hour period (ie, at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours). The 750 mg dose of desvenlafaxine was used to provide a preliminary examination of the effect of food on the pharmacokinetics of desvenlafaxine. This dose was first given under fed conditions, and then, subsequently in a second group of subjects, following an overnight fast of at least 8 hours.

Study 3 (Wyeth Research Clinical Pharmacology Unit; Philadelphia, PA) was a double-blind, placebo-controlled, sequential group, multiple-ascending-dose study conducted to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of desvenlafaxine 300, 450, and 600 mg. Each dose level was evaluated in 12 subjects (9 subjects receiving desvenlafaxine and 3 receiving placebo). Each subject participated in only 1 dose group and received multiple dose administrations of either desvenlafaxine or placebo. The study included a screening evaluation that occurred within 3 weeks of test article administration, an 18-day (17-night) inpatient period, and an end-of-study evaluation after the last pharmacokinetic blood sample had been collected. Subjects were administered test articles once daily for a total of 14 days, 30 minutes after consuming a medium-fat breakfast. On study day 1, blood samples were collected prior to test article administration, and multiple timed blood samples were taken for pharmacokinetic analysis following single-dose test article administration (i.e., 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours). Blood samples were also collected on days 3, 4, 5, 7, 10, and 13 and analyzed for trough concentrations. Finally, multiple timed blood samples were taken for pharmacokinetic analysis in the 72-hour period following the final administration of test article on day 14.

Safety and tolerability

Safety and tolerability were assessed in all studies through the monitoring and recording of adverse events (AEs). Additionally, physical examinations, ECGs, and laboratory and vital sign assessments were conducted. In studies 2 (single-ascending dose) and 3 (multiple-ascending dose), a visual analog scale (VAS) was used to measure the severity of nausea and assess the tolerability of the treatment.

Desvenlafaxine/Venlafaxine assays

Assays for desvenlafaxine and venlafaxine were performed by Bioassay Laboratory, Inc (Houston, TX).

In studies 1 (single-dose proportionality), 2 (single-ascending dose) and 3 (multiple-ascending dose) a high performance liquid chromatography (HPLC) method with fluorescence detection was utilized. For study 2, measurement of venlafaxine concentrations was included in addition to measurement of desvenlafaxine concentrations. HPLC was performed using propranolol hydrochloride as an internal standard. Eight different standard concentrations were used for the calibration curve. A single calibration curve was analyzed with each batch run. QC samples were prepared at concentrations of 15.0 ng/mL, 60.0 ng/mL, and 300.0 ng/mL for venlafaxine and desvenlafaxine with two sets of QC samples assayed with each run. Desvenlafaxine and venlafaxine were 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 0.01 N hydrochloric acid solutions; 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/minute (± 20%), and autosampler run time was 25 minutes. The retention times for venlafaxine and desvenlafaxine were 17.4 minutes (± 20%) and 12.7 minutes (± 20%), respectively. The wavelengths used were EX 230 nm and EM 300 nm. Data were collected and calculated on a Waters

Millennium 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 desvenlafaxine and venlafaxine was 5.0 ng/ml plasma, and the upper limit of quantitation was 500 ng/mL for both venlafaxine and desvenlafaxine.

Pharmacokinetic analysis

The desvenlafaxine plasma concentration data for each subject were analyzed using noncompartmental pharmacokinetic methods in studies 1 (single-dose proportionality), and 3 (multiple-ascending dose). In study 2 (single-ascending dose), both venlafaxine and desvenlafaxine plasma concentration data for each subject were analyzed by noncompartmental pharmacokinetic methods.

In all studies, the peak drug concentration (C_{max}) and time of peak concentration (T_{max}) were taken directly from the observed data. The apparent terminal-phase disposition rate constant (λ_z) was estimated by a log-linear regression of plasma concentrations determined to be in the log-linear elimination phase by visual inspection. The apparent terminal-phase elimination half-life ($t_{1/2}$) was calculated as $t_{1/2}=0.693/\lambda_z$. The area under the single-dose plasma concentration-time curve (AUC_T) truncated at the last observed plasma concentration at time T (C_T) was calculated using the log-trapezoidal rule for decreasing concentrations and the linear-trapezoidal rule for increasing concentrations. Total area under the plasma concentration-time curve (AUC) was then estimated by $AUC=AUC_T + C_T/\lambda_z$. Apparent oral-dose clearance (Cl/F) was calculated as dose/AUC, and apparent volume of distribution (V_Z/F) was calculated as $(Cl/F)/\lambda_z$. For the multiple-dose pharmacokinetic analysis, the area under the steady-state plasma concentration-time curve (AUCss) estimated over the dose administration interval (τ=24 h) was calculated by using the log-trapezoidal rule with the observed data; Cl/F was calculated as Cl/F=dose/AUCss.

Pharmacodynamics

Serotonin and norepinephrine assays: Blood and plasma samples from subjects in study 2 (single-ascending dose) were sent to Service de Biochimie-Pharmacologie-Toxicologie, Hopital A Mignot, Versailles, France. Using validated bioanalytical methods, serotonin levels were measured in blood and plasma, while norepinephrine levels were only measured in plasma. The minimum quantifiable concentration was approximately 0.5 ng/ml for serotonin and 75 pg/ml for norepinephrine.

Whole blood and plasma serotonin levels were determined using an ion-paired, reversed phase HPLC with coulometric detection [6]. Norepinephrine plasma levels were determined using a HPLC method with coulometric detection [7,8].

Visual analog scale for nausea: The intensity of nausea over time was evaluated using a VAS at specified times during study 2 (single-ascending dose) and study 3 (multiple-ascending dose). Subjects placed a mark on a 100 mm line that represented a scale from no nausea (far left) to the maximum nausea ever experienced (far right). The VAS for nausea was scored as the distance in millimeters from the left side of the VAS line to the subject's mark.

Cognitive tests

Subjects' vigilance and psychomotor performance were assessed in study 2 (single-ascending dose) by the choice reaction time (CRT) using the Leeds Psychomotor Test [9], the digit symbol substitutions test (DSST), and a test for long- and short-term memory (immediate and delayed free recall of a 15-word list). Subjects in study 3 (multiple-ascending dose) were evaluated with the DSST and memory tests, using a 20-word list with immediate and delayed free recall. Psychomotor performance was assessed before dose administration and at 2 hours and 7 hours after dose administration on study day 1. Memory was assessed 3 hours after dose administration on days 1 and 13.

Electroencephalogram measurements

On day 1 in study 2, a daytime spectral analysis of electroencephalogram (EEG) data was performed prior to dose administration, then 2 hours and 7 hours after dose administration. Recording was performed using 4 bipolar leads (right frontotemporal (F4T4), left frontotemporal (F3T3), right temporooccipital (T4O2), and left temporooccipital (T3O1)). During the 5 minute recording, the subject was in a resting condition with eyes closed.

The absolute total power and the absolute power in delta (0 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 12 Hz), beta-1 (12 to 20 Hz), beta-2 (21 to 30 Hz) and mean frequencies were collected. The relative power was calculated as the absolute power of each delta, theta, alpha, beta-1, and beta-2 divided by the absolute total power.

Statistical analysis

For all 3 studies, values for dose-dependent pharmacokinetic parameters (eg, C_{max}, AUC) were normalized to the lowest dose before performing statistical comparisons. The statistical comparisons of mean desvenlafaxine plasma concentrations at each sampling time and pharmacokinetic parameters of desvenlafaxine were compared among the different study arms using an analysis of variance. In addition, the linear dose proportionalities of the C_{max}, AUC, and AUC_{ss} were assessed using an exponential regression model that measures the degree of nonlinear proportionality.

There were no statistical comparisons of safety data among dose groups for study 1. In studies 2 and 3, the safety (vital signs, ECG parameters, and routine laboratory tests) and pharmacodynamic parameters (EEG, psychometric parameters, and biomarkers) were analyzed using an analysis of covariance with the preadministration data as the baseline covariant and a factor for treatment. Before EEG data were analyzed, the absolute and relative parameters for EEG were checked for normality. The residuals from the absolute parameters were not normally distributed; therefore, a log transformation of the values was calculated before any statistical analyses. The statistical comparisons of the nausea VAS raw scores and the VAS pharmacodynamics parameters among the different groups were analyzed using 1-factor analysis of variance. All tests of hypotheses were 2-sided with α level of 0.05.

Results

Subjects

Demographic characteristics of the subjects in all studies are summarized in table 1. There was wide ethnic variability between the studies (Study 1: black=54%, Caucasian=21%; Study 2: Caucasian=100%; Study 3: black=33%, Caucasian=56%).

Pharmacokinetics

After administration of single doses of desvenlafaxine in studies 1 and 2, desvenlafaxine was slowly absorbed, with the mean T_{max} values occurring between 5 and 8 hours after administration (Tables 2 and 3;

	Study 1. Single-Dose Proportionality Study	Study 2. Single-Ascending-Dose Study									
	Desvenlafaxine	Desvenlafaxine								Venlafaxine ER	Placebo	Total
Characteristic	100, 300, and 600 mg (n=24)	150 mg (n=6)	255 mg (n=6)	300 mg (n=6)	450 mg (n=6)	600 mg (n=6)	750 mg (n=5)	750 mg (fasted) (n=6)	900 mg (n=6)	150 mg (n=16)	(n=16)	(n=79)
Age (years)												
Mean ± SD	35.0 ± 8.5	31.5 ± 8.3	26.2 ± 4.6	27.5 ± 7.6	28.5 ± 5.6	27.0 ± 4.7	23.6 ± 4.0	24.3 ± 3.3	27.5 ± 9.0	27.6 ± 7.2	27.9 ± 6.9	27.4 ± 6.5
Sex, n (%)												
Male	23 (96)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (100)	6 (100)	6 (100)	16 (100)	16 (100)	79 (100)
Ethnic origin, n (%)												
Black	13 (54)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	6 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Caucasian	5 (21)	6 (100)	6 (100)	6(100)	6 (100)	6 (100)	5 (100)	6 (100)	6 (100)	16 (100)	16 (100)	79 (100)
Weight (kg)												
Mean ± SD	80 ± 11	76.7 ± 7.5	72.8 ± 11.2	73.8 ± 8.2	70.3 ± 6.7	72.0 ± 6.4	72.2 ± 7.4	72.8 ± 6.8	77.5 ± 7.7	72.3 ± 8.3	74.8 ± 10.6	73.6 ± 8.4

	Study 3. Multiple-Ascending-Dose Study				
	Desvenlafaxine			Placebo	Total
	300 mg (n=9)	450 mg (n=9)	600 mg (n=9)	(n=9)	(n=36)
Age (years)					
Mean ± SD	34.0 ± 5.4	34.9 ± 7.4	32.9 ± 4.7	34.7 ± 6.6	34.1 ± 5.9
Sex, n (%)					
Male	9 (100)	9 (100)	9 (100)	9 (100)	36 (100)
Ethnic origin, n (%)					
Black	3 (33)	8 (89)	2 (22)	3 (33)	16 (44)
Other	1 (11)	1 (11)	3 (33)	1 (11)	6 (17)
Caucasian	5 (56)	0	4 (44)	5 (56)	14 (39)
Weight (kg)					
Mean ± SD	83.0 ± 10.3	80.8 ± 10.1	t79.6 ± 13.3	81.7 ± 6.3	81.3 ± 9.9

ER, extended release; SD, standard deviation

Table 1: Demographic and Baseline Characteristics of Studies 1 (Single-Dose Proportionality), 2 (Single-Ascending Dose), and 3 (Multiple-Ascending Dose).

Treatment	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
100 mg	234 171-326	7.28 4.0-12.0	11.1 9.1-14.2	5376 2649-7516	0.236 0.146-0.523
300 mg	701 474-938	7.01 4.0-12.0	10.9 8.9-14.2	16215 10195-21958	0.233 0.156-0.331
600 mg	1409 1147-1992	8.11 6.0-12.0	11.0 8.4-14.2	34880 23572-46829	0.218 0.141-0.302
3-Period Crossover Analysis of Variance Log-Transformed Data[b]					
Sequence	<0.001	0.735	0.008	<0.001	<0.001
Subject (sequence)	<0.001	0.367	<0.001	<0.001	<0.001
Treatment	0.759	0.226	0.670	0.121	0.121
Period	0.960	0.894	0.767	0.564	0.564

AUC, area under the plasma concentration-time curve; Cl/F, apparent oral-dose clearance; C_{max}, peak drug concentration; T_{max}, time of peak concentration; $t_{1/2}$, terminal-phase elimination half-life.
[a]Data shown is geometric mean, minimum – maximum.
[b]Before statistical comparisons were made, dose-dependent values (C_{max} and AUC) were normalized to the lowest dose.

Table 2: Desvenlafaxine Pharmacokinetic Parameters,[a] Study 1 (Single-Dose Proportionality Study).

Figure 1). In study 3, single dose T_{max} values occurred between 7 and 9 hours after desvenlafaxine administration. Following multiple doses of desvenlafaxine in study 3 (Table 4; Figure 2), mean T_{max} values occurred between 4 and 6 hours after dosing. Desvenlafaxine was also slowly eliminated, with a mean $t_{1/2}$ of 9 to 11 hours following both single doses (studies 1 and 2) and multiple doses (study 3) of desvenlafaxine.

In study 1 (single-dose proportionality), the mean desvenlafaxine T_{max}, $t_{1/2}$, and Cl/F were similar across the 3 treatments (Table 2). There was a linear increase in desvenlafaxine AUC and C_{max} after administration of 100, 300, and 600 mg doses. There was a 3-fold increase in both C_{max} and AUC from the 100 to the 300 mg dose, and there was an approximately 6-fold increase in both C_{max} and AUC from 100 to 600 mg dose.

In study 2, with the exception of desvenlafaxine C_{max}, no statistically

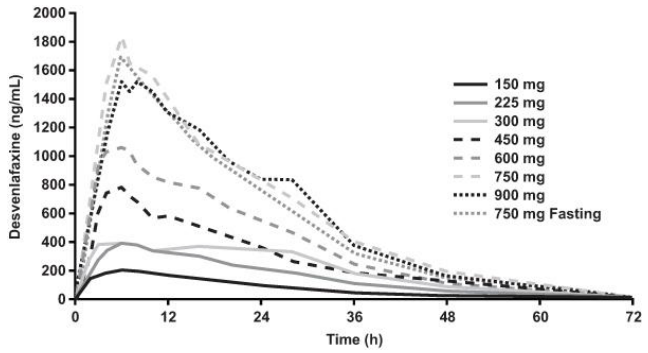

Figure 1: Study 2 (Single-Ascending-Dose Study): Desvenlafaxine Plasma Concentration. Desvenlafaxine was slowly absorbed after a medium fat breakfast consumed 10 minutes before test article administration (geometric mean t_{max}, 5 to 7 hours).

significant differences were found among the dose groups in any of the dose-normalized, single-dose pharmacokinetic parameters. Although desvenlafaxine C_{max} values were consistent among 6 of the 7 desvenlafaxine postprandial dose groups, the 750 mg group exhibited a higher mean C_{max} than predicted from the other groups.

In a linear trend analysis, the higher-than-expected C_{max} and AUC values in the postprandial desvenlafaxine 750 mg group imparted a slight nonlinearity in the increases in desvenlafaxine C_{max} and AUC with increasing dose; values were 10% to 15% higher than predicted from a linear dose relationship. Given the minor degree of observed nonlinearity, C_{max} and AUC can be considered to increase in an approximately linear manner with increasing dose over the range of 150 to 900 mg. Administration of desvenlafaxine 750 mg with a medium-fat meal produced minor increases in desvenlafaxine C_{max} and AUC compared with fasting administration, but the meal did not alter the slow release characteristics of the desvenlafaxine formulation.

For study 3 (multiple-ascending dose) desvenlafaxine trough plasma concentrations were assessed on days 3, 4, 5, 7, 10 and 13 following daily oral doses of 300 and 450 mg. Because administration of the 600 mg dose was stopped on or before study day 8 due to transient postural hypotension in 6 subjects, desvenlafaxine trough plasma concentrations were taken only through day 7 for the 600 mg dose. An examination of trough plasma concentrations indicated that pharmacokinetic steady-state was reached by day 4 or day 5. The steady-state 24 hour AUCs measured on day 14 after multiple doses of 300 and 450 mg Q24h of 14577 ng.h/mL and 23418 ng.h/mL, respectively (Table 4), were found to be in reasonable agreement with the 300 and 450 mg single-dose AUCs (15239 ng.h/mL and 19938 ng.h/mL, respectively) (Figure 2). Therefore, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

Pharmacodynamic results

Norepinephrine and serotonin concentrations in blood and plasma: In study 2 (single-ascending dose), desvenlafaxine doses of 600 mg or higher resulted in a significant increase in mean norepinephrine plasma concentrations compared with placebo (Figure 3). The magnitude of differences in norepinephrine plasma concentrations between placebo values and desvenlafaxine 600 to 900 mg values were similar at 2 and 7 hours postdose. Venlafaxine ER 150 mg did not alter the concentrations of norepinephrine in plasma.

Administration of any dose of desvenlafaxine or venlafaxine ER 150 mg did not result in significant changes in serotonin concentrations in plasma or whole blood. However, 39 of 69 subjects had a predose plasma concentration above the normal range (0.3 to 3.0 ng/mL), drawing into question the processing of samples in this assay. Although these findings should be interpreted cautiously due to the small number of samples, an analysis of samples from subjects whose predose serotonin levels were within the normal range revealed a significant difference in plasma levels among the treatments at 7 hours postdose.

Treatment	n	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	Cl/F (L/h/kg)
Venlafaxine ER 150 mg Postprandial and Fasting	16	166.4 77.0-246.8	7.9 6.0-10.0	12.2 8.0-19.0	4503 2535-6634	0.46 0.35-0.74
Desvenlafaxine						
150 mg Postprandial	6	203.5 118.7-346.0	4.5 2.0-10.0	9.1 8.1-11.8	4838 3344-6358	0.41 0.26-0.64
225 mg Postprandial	6	421.0 292.2-609.3	6.6 4.0-16.0	11.1 8.4-14.6	10202 5950-14622	0.31 0.26-0.42
300 mg Postprandial	6	444.9 393.7-486.8	7.1 2.0-28.0	10.3 7.2-12.0	14258 10760-17819	0.29 0.20-0.42
450 mg Postprandial	6	807.8 562.8-984.9	4.9 4.0-6.0	10.1 9.1-11.3	18278 14344-23824	0.35 0.29-0.43
600 mg Postprandial	6	1084.3 884.0-1337.8	5.2 4.0-7.0	10.2 8.8-11.2	26098 19635-42078	0.32 0.20-0.39
750 mg Postprandial	5[b]	1868.5 1431.7-2346.0	5.8 4.0-8.0	9.9 8.8-10.4	41478 36269-50949	0.26 0.23-0.30
900 mg Postprandial	4[c]	1540.9 1080.9-1830.9	7.2 6.0-8.0	9.6 8.6-10.9	37758 27392-45854	0.31 0.23-0.48
750 mg Fasting	6	1658.6 1225.0-2054.6	6.8 6.0-8.0	9.5 7.8-11.2	36349 28669-43664	0.28 0.23-0.39
1-Factor ANOVA of Log-Transformed Data (Desvenlafaxine Postprandial Data Only)[d]						
Treatment		0.015	0.667	0.408	0.063	0.144

ANOVA, analysis of variance; AUC, area under the plasma concentration-time curve; Cl/F, apparent oral-dose clearance; C_{max}, peak drug concentration; ER, extended release; $t_{1/2}$, terminal-phase elimination half-life; T_{max}, time of peak concentration.
[a]Data shown are geometric mean, minimum-maximum.
[b]Excluding 1 subject who vomited and exhibited very low plasma concentrations.
[c]Excluding 2 subjects who vomited and exhibited very low plasma concentrations.
[d]Before statistical comparisons, C_{max} and AUC were normalized to the lowest dose.

Table 3: Desvenlafaxine Pharmacokinetic Parameters,[a] Study 2 (Single-Ascending-Dose Study).

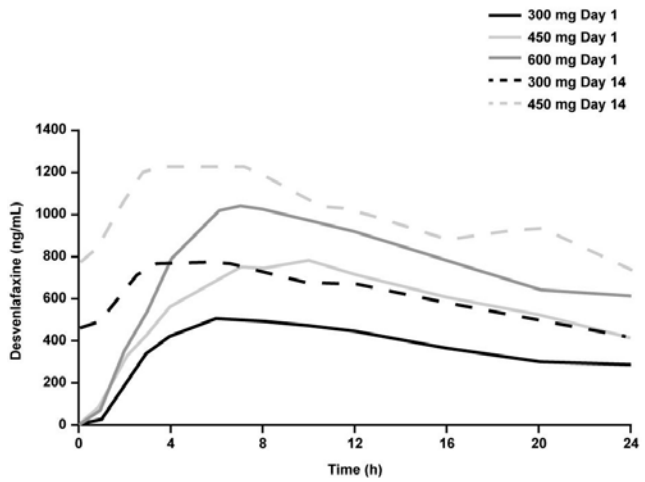

Figure 2: Study 3 (Multiple-Ascending-Dose Study): Plasma Concentration Curves. Mean t_{max} occurred between 6 and 8 hours after dose administration and was slowly eliminated with a mean $t_{1/2}$ of 15 to 18 hours. No significant differences in any of the pharmacokinetic parameters were found among the doses.

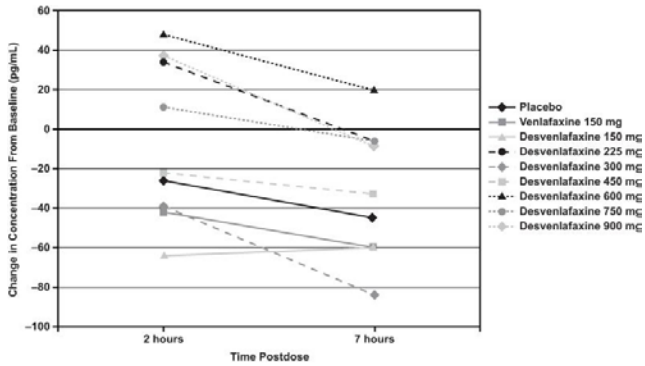

Figure 3: Study 2 (Single-Ascending-Dose Study): Change in Mean Norepinephrine Plasma Concentrations. Healthy subjects receiving a single dose of placebo, venlafaxine, or desvenlafaxine showed a significant increase in mean norepinephrine plasma concentration with desvenlafaxine doses of 600 mg or higher when compared with placebo.

The highest mean and mean change from baseline values occurred with the venlafaxine 150 mg dose and desvenlafaxine 225 and 450 mg doses.

Visual analog scale for nausea: In study 2 (single-ascending dose), only 1 of the 16 subjects receiving placebo reported a single score >0 mm. VAS nausea scores generally rose with increasing doses of desvenlafaxine; however, no subjects reported a single VAS score >0 mm in the 600 mg dose group, and all subjects in the 750 mg fed group reported VAS ≥ 10 mm.

In study 3 (multiple-ascending dose), the overall difference in maximum VAS nausea scores among the groups was not significant, despite numerically higher maximum VAS scores in the 450 and 600 mg dose groups compared with the 300 mg dose group. All subjects accommodated to the nausea after the first day in the 300 mg dose group and by the seventh day for the 450 mg dose group.

Choice reaction time: Desvenlafaxine did not affect total CRT (recognition plus motor times) over the range of doses tested for subjects in study 2 (single-ascending dose). The baseline, measured as values for total CRT, was similar among the groups, and there were no statistically significant differences in the mean total CRT at 2 hours and 7 hours after dose administration (p=0.525 and p=0.319, respectively). Desvenlafaxine also had no significant effect on the recognition or motor components of the total CRT (data not shown).

Digit symbol substitution test: In study 2 (single-ascending dose), desvenlafaxine did not significantly affect DSST scores over the dose range studied, and no trend for DSST scores to increase or decrease with dose was detected. In study 3 (multiple-ascending dose), the 300 mg dose group scored somewhat better at later time points than at baseline, whereas the 450 mg, 600 mg, and placebo groups produced similar scores at all time points. All pairwise comparisons were exploratory, but they indicated that the 300 mg dose group performed significantly better in the DSST than the placebo group on day 1 (hour 7) (p=0.027) and day 13 (preadministration) (p=0.019). At other time points, the 300 mg group appeared to have higher mean DSST scores than the placebo group, but these observed differences did not attain statistical significance.

Word-recall tests: Following test article administration in study 2 (single-ascending dose) and study 3 (multiple-ascending dose), there were no significant differences among the treatment groups in terms of immediate or delayed word recall. In study 3, the mean percentage of words retained (number of words recalled after an approximate 30 minute delay divided by number of words recalled immediately after their presentation) ranged from 54% (450 mg) to 76% (placebo) at 3 hours postdose, and 72% (placebo) to 86% (300 mg) at 13 days postdose. A trend analysis of the immediate- and delayed-word-recall tests found no dose effect.

Electroencephalograph results: In study 2 (single-ascending dose), a trend analysis of EEG data demonstrated a significant increase in relative slow beta in F3T3 at desvenlafaxine doses 600 mg and higher, in relative fast beta in F3T3 at desvenlafaxine doses 225 mg and higher, in absolute slow and fast beta in F4T4, and in absolute theta and fast beta in T4O2 after the desvenlafaxine 900 mg dose.

Pairwise comparisons indicated significant increases in absolute beta energies in all EEG leads with desvenlafaxine doses of 450 mg or greater, particularly in the frontotemporal lobes, where beta is more pronounced. These increases were associated with decreases in the lower EEG ranges. Interestingly, the changes in fast beta were more pronounced at 2 hours than at 7 hours postdose, and thus did not correspond with plasma desvenlafaxine C_{max} values. Compared with placebo, venlafaxine 150 mg did not produce any significant changes in EEG results.

Safety and tolerability: In study 1 (single-dose proportionality), 17 of the 24 subjects (71%) reported at least 1 treatment-emergent adverse event (TEAE). The overall incidence of TEAEs was 65% in the 600 mg group, 40% in the 300 mg group, and 18% in the 100 mg group The most frequently reported TEAEs (>30%) in all treatment groups were nausea (12/24; 50%) and dizziness (11/24; 46%), which occurred more frequently in the 300 and 600 mg desvenlafaxine groups than the 100 mg group. Two of the 24 subjects (8%) withdrew because of AEs. One subject with no history of seizures developed a partial (focal) seizure approximately 50 minutes after receiving desvenlafaxine 600 mg, a serious AE which resolved without intervention. The second subject developed symptomatic hypotension approximately 20 minutes after receiving desvenlafaxine 100 mg, which resolved with administration of fluids.

In study 2 (single-ascending dose), 28 out of 79 (35%) subjects

reported 1 or more TEAEs during this study. TEAEs were more common at the 750 mg dose (100% in fed subjects) and 900 mg dose (83%) than at lower doses (Table 5). The maximum tolerated dose (MTD) of desvenlafaxine was 750 mg, due to the occurrence of vomiting in more than half (4/6) of the subjects receiving the 900 mg dose. In comparison, 3 of 11 subjects receiving desvenlafaxine 750 mg reported vomiting, and none of the 30 subjects receiving doses of desvenlafaxine less than 750 mg reported vomiting. Severe nausea (VAS score ≥ 67) was reported by 33% of subjects who took the 900 mg dose, by 0% of fed subjects who took the 750 mg dose, and by 17% of fasting subjects who took the 750 mg dose, compared with 6% of subjects receiving venlafaxine 150 mg. Thirty-five of the 36 subjects in study 3 (multiple-ascending dose) had TEAEs, most of which were mild (Table 6). The MTD was 450 mg/d due to dose-limiting orthostatic hypotension in 6 subjects receiving the 600 mg dose. Orthostatic hypotension was not reported by any subject at doses ≤ 450 mg/d. Nausea was reported in 44%, 67%, and 78% of subjects receiving 300, 450, and 600 mg, respectively. The most common AEs in subjects receiving desvenlafaxine 300 mg were hypertension and nausea, whereas the most common AEs in subjects receiving desvenlafaxine 450 mg were hypertension, nausea, headache, constipation, and tachycardia. The most common TEAEs in subjects receiving 600 mg were abnormal dreams, anorexia, asthenia, constipation, dizziness, euphoria, hypertension, nausea, postural hypotension, tachycardia, and twitching.

Discussion

The purpose of these studies was to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of desvenlafaxine. These results allowed for determination of dose-limiting AEs and the MTD. Previous studies of subjects taking SNRIs such as duloxetine showed nausea and orthostatic hypotension to be the potentially dose-limiting AEs for these agents [10-12]. The studies reported here show that the incidence of nausea with desvenlafaxine treatment was dose-related, with the percentage of subjects experiencing nausea generally increasing with the dose level. In study 2, only 1 subject each among those who received single-dose administration of desvenlafaxine 100 mg and 150 mg experienced nausea, which was mild and transient in nature. In contrast, 17% and 33% of subjects receiving single-dose administration of 750 mg (under fasting conditions) and 900 mg desvenlafaxine, respectively had severe nausea. With multiple-dose administration, nausea occurred in more than 40% of subjects at each desvenlafaxine dose level. However, nausea was not reported after the first day in the 300 mg multiple-dose group and after the seventh day in the 450 mg multiple-dose group.

Results from the single-ascending-dose study determined the MTD of desvenlafaxine to be 750 mg, due to the high incidence of vomiting at the 900 mg dose level. The MTD in the multiple-ascending-dose study was 450 mg, due to a high incidence of orthostatic hypotension at the 600 mg dose level. Neither of the dose-limiting AEs occurred in subjects receiving a single dose of 150 mg or multiple doses of 300 mg. AEs occurring at doses below the MTD were mild to moderate and generally resolved quickly. As the recommended therapeutic 50 mg dose of desvenlafaxine for MDD is considerably lower than the single-dose and multiple-dose MTD, these data suggest that desvenlafaxine will have a favorable safety and tolerability profile with clinical use.

Desvenlafaxine Dosage	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	$t_{1/2}$ (h)	AUC_{ss} (ng•h/mL)	Cl/F (L/h/kg)
300 mg	796 566-1067	4.4 3-6	408 268-567	10.8 7.8-15.0	14577 10856-18429	0.25 0.16-0.35
450 mg	1339 959-1677	6.4 3-20	670 433-902	11.3 8.9-15.3	23418 16649-29915	0.25 0.17-0.35
p values from the 1-factor ANOVA with log-transformed parameters[a]						
	0.228	0.118	0.519	0.711	0.556	0.963

ANOVA, analysis of variance; AUC_{ss}, area under the steady-state plasma concentration-time curve; Cl/F, apparent oral-dose clearance; C_{max}, peak drug concentration; C_{min}, minimal drug concentration; SD, standard deviation; $t_{1/2}$, terminal-phase elimination half-life; T_{max}, time of peak concentration.
[a]Data shown are geometric mean, minimum-maximum.
[b]Prior to statistical comparisons, dose-dependent parameters (C_{max}, C_{min} and AUC_{ss}) were dose-normalized to the 300-mg dose.

Table 4: Desvenlafaxine Multiple-Dose (Day 14) Pharmacokinetic Parameters,[a] Study 3 (Multiple-Ascending-Dose Study).

Body System	Desvenlafaxine								Venlafaxine	Placebo
	150 mg (n=6)	225 mg (n=6)	300 mg (n=6)	450 mg (n=6)	600 mg (n=6)	750 mg (n=5)	750 mg fasted (n=6)	900 mg (n=6)	150 mg (n=16)	(n=16)
Any adverse event	2 (33)	2 (33)	2 (33)	2 (33)	0	5 (100)	4 (67)	5 (83)	5 (31)	1 (6)
Digestive										
Nausea	1 (17)	2 (33)	2 (33)	2 (33)	0	5 (100)	3 (50)	5 (83)	4 (25)	0
Nausea (severe)	0	0	0	0	0	0	1 (17)	2 (33)	1 (6)	0
Vomiting	0	0	0	0	0	2 (40)	1 (17)	4 (67)	1 (6)	0
Nervous										
Dizziness	1 (17)	0	0	0	0	0	2 (33)	0	0	0
Feeling drunk	1 (17)	0	0	0	0	0	1 (17)	2 (33)	0	0
Paresthesia	0	0	0	0	0	2 (40)	0	0	0	0
Respiratory										
Yawn	0	0	0	0	0	2 (40)	0	0	0	0
Skin/appendages										
Sweating	0	0	0	0	0	0	0	2 (33)	0	0

Table 5: Frequency of Treatment-Emergent Adverse Events (number [%]) Reported for 2 or More Subjects in any Treatment Group in Study 2 (Single-Ascending-Dose Study).

Body System	Desvenlafaxine			Placebo
	300 mg (n=9)	450 mg (n=9)	600 mg (n=9)	(n=9)
Any adverse event	8 (89)	9 (100)	9 (100)	9 (100)
Body as a whole				
Asthenia	0	1 (11)	4 (44)	0
Headache	1 (11)	4 (44)	0	2 (22)
Cardiovascular				
Hypertension				
Postural hypotension	5 (56)	8 (89)	8 (89)	1 (11)
Tachycardia	0	0	6 (67)	0
Tachycardia sinus	2 (22)	4 (44)	9 (100)	3 (33)
Vasodilation	0	2 (22)	0	0
Ventricular extrasystoles	0	2 (22)	1 (11)	0
	0	1 (11)	2 (22)	0
Digestive				
Anorexia				
Constipation	0	0	4 (44)	0
Nausea	2 (22)	3 (33)	4 (44)	0
Vomiting	4 (44)	6 (67)	7 (78)	1 (11)
	0	2 (22)	2 (22)	0
Metabolic and nutritional				
CPK increased				
ALT increased	2 (22)	0	0	1 (11)
	0	2 (22)	0	1 (11)
Nervous				
Abnormal dreams	0	0	4 (44)	0
Anxiety	1 (11)	0	2 (22)	0
Depersonalization	0	0	2 (22)	0
Dizziness	2 (22)	1 (11)	3 (33)	0
Euphoria	0	0	3 (33)	0
Insomnia	1 (11)	0	2 (22)	0
Nervousness	0	0	2 (22)	0
Tremor	0	0	2 (22)	0
Trismus	0	0	2 (22)	0
Twitching	1 (11)	0	3 (33)	0
Respiratory				
Rhinitis				
	0	0	0	2 (22)
Skin/appendages				
Application site reaction				
Sweating	0	0	5 (56)	4 (44)
	0	0	2 (22)	0
Urogenital				
Dysuria				
Impotence	0	0	2 (22)	0
	0	0	2 (22)	0

ALT, alanine aminotransferase; CPK, creatine phosphokinase

Table 6: Frequency of Treatment-Emergent Adverse Events (Number [%]) Reported for 2 or More Subjects in Any Treatment Group in Study 3 (Multiple-Ascending-Dose Study).

The pharmacokinetic analyses of these studies show slow absorption and elimination phases. Formal statistical testing showed that the pharmacokinetic profile of desvenlafaxine is linear and dose proportional at doses ranging from 100 to 600 mg daily. Furthermore, multiple-dose pharmacokinetics was adequately predicted from single-dose pharmacokinetics, and there was no significant effect of food on the pharmacokinetics of a single dose of desvenlafaxine 750 mg. The lack of effect of food intake on the pharmacokinetics of desvenlafaxine suggests that food intake may not be a factor in its clinical administration.

The pharmacodynamics of desvenlafaxine were evaluated using a number of methods, including norepinephrine concentrations in plasma, DSST, CRT, a battery of word-recall tests, and EEG. In the single-ascending-dose study, desvenlafaxine doses of 600 mg or higher were found to significantly increase mean norepinephrine plasma concentrations, compared with placebo, at both 2 hours and 7 hours postdose. However, the protocol did not require that subjects be calm and rested prior to and during the collection of the blood samples; thus, the measurement of increases in plasma norepinephrine following desvenlafaxine increases may not have been performed under optimal conditions [13]. Significant increases in absolute beta energies in all EEG leads were seen with desvenlafaxine doses of 450 mg or greater, particularly in the frontotemporal lobes; interestingly, changes in fast beta energy did not correspond with plasma desvenlafaxine C_{max} values. Although not observed with venlafaxine in this study, a similar EEG effect, ie, increase in fast beta waves, has previously been observed with venlafaxine [14,15], as well as with other antidepressants, particularly those with a mechanism of action involving both serotonin and norepinephrine [15]. Neither a single dose of desvenlafaxine 150 mg nor a single dose of venlafaxine 150 mg significantly altered recognition, motor or total reaction-time scores for the CRT, nor did they affect DSST scores or word recall. In the multiple-ascending-dose study, there were no significant differences among the 3 desvenlafaxine

dose groups and the placebo group in terms of DSST scores or word recall. In 2 previous studies that used a 90-second version of the DSST, administration of venlafaxine immediate release 50 mg every 8 hours (150 mg/d) did not significantly affect DSST score [16,17].

Conclusion

These trials have demonstrated the MTD for desvenlafaxine as 750 mg for a single dose and 450 mg for multiple doses. Desvenlafaxine was not associated with significant alterations in psychomotor function or memory. Desvenlafaxine was slowly absorbed and eliminated with approximately linear pharmacokinetics across the wide range of single and multiple doses studied.

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