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TITLE PAGE

An Assessment of Drug-Drug Interactions: The Effect of Desvenlafaxine and Duloxetine on the Pharmacokinetics of the CYP2D6 Probe Desipramine in Healthy Subjects

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Abbreviations: CYP, cytochrome P450; BID, twice daily; AUC, area under the plasma concentration-versus-time curve; C_{max}, peak plasma concentration; ODV, O-desmethylvenlafaxine; MDD, major depressive disorder; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AE, adverse event; PCR, polymerase chain reaction; LC/MS/MS, liquid chromatography/tandem mass spectrometry; QC, quality control; t_{max}, time to peak concentration; $t_{1/2}$, apparent terminal-phase elimination half-life; Cl/F, apparent oral-dose clearance; LSG, least square geometric; PCI, potentially clinically important.

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ABSTRACT

A number of antidepressants inhibit activity of the cytochrome P450 (CYP) 2D6 enzyme system, which can lead to drug-drug interactions. Based on its metabolic profile, desvenlafaxine, administered as desvenlafaxine succinate, a new serotonin-norepinephrine reuptake inhibitor, is not expected to impact activity of CYP2D6. This single-center, randomized, open-label, 4-period, crossover study was undertaken to evaluate the effect of multiple doses of desvenlafaxine (100 mg/d, twice the recommended therapeutic dose for major depressive disorder in the US) and duloxetine (30 mg BID) on the pharmacokinetics of a single dose of desipramine (50 mg). Single-dose of desipramine was first given to assess its pharmacokinetics. Desvenlafaxine or duloxetine was then administered, in a crossover design, so that steady-state levels were achieved; a single dose of desipramine was then coadministered. The geometric least square mean ratios (coadministration vs desipramine alone) for area under the plasma concentration-versus-time curve (AUC) and peak plasma concentrations (C_{max}) of desipramine and 2-hydroxydesipramine were compared using analysis of variance. Relative to desipramine alone, increases in AUC and C_{max} of desipramine associated with duloxetine administration (122%/63%, respectively) were significantly greater than those associated with desvenlafaxine (22%/19%, respectively; $P<0.001$). Duloxetine coadministered with desipramine was also associated with a decrease in 2-hydroxydesipramine C_{max} that was significant compared to the small increase seen with desvenlafaxine and desipramine (–24% vs 9%; $P<0.001$); the difference between changes in 2-hydroxydesipramine AUC did not reach statistical significance ($P=0.054$). Overall, desvenlafaxine had a minimal impact on pharmacokinetics of desipramine compared with duloxetine, suggesting lower risk for CYP2D6-mediated drug interactions.

INTRODUCTION

Concomitant use of a drug that affects the activity of the same cytochrome P450 (CYP) enzyme system responsible for biotransformation of another drug can lead to significant elevations in plasma concentration and potentially important drug-drug interactions (Preskorn and Flockhart, 2004). Such interactions may be associated with poor tolerability or increased risk for toxicity. In addition, for drugs requiring biotransformation via CYP enzymes from an inactive/less active parent compound to a pharmacologically active metabolite, drug interactions may manifest as a reduction in efficacy (Preskorn and Flockhart, 2004; Stearns et al., 2003; Preskorn and Werder, 2006). Drug interactions impact clinical care and may create the need for dose adjustments, consideration of different therapeutic options, or other management strategies.

Several antidepressants are known to inhibit CYP2D6 activity (Zanger et al., 2004). The selective serotonin reuptake inhibitors are associated with varying degrees of CYP2D6 inhibition. For example, paroxetine and fluoxetine strongly inhibit CYP2D6 (K_i of 2.0μM and 3.0μM, respectively), while citalopram and sertraline have been shown to be moderate or weak inhibitors (K_i of 19μM and 22.7μM, respectively) (Preskorn, 2003; Preskorn et al., 2007a; Skjelbo and Brosen, 1992; von Moltke et al., 1995). CYP2D6 is responsible for the metabolism of drugs (and activation of prodrugs) commonly used to treat various medical conditions; some examples include the antiestrogen tamoxifen (Stearns et al., 2003), the atypical opioid tramadol (Laugesen et al., 2005; Mason and Blackburn, 1997), the antiarrhythmic amiodarone (Fukumoto et al., 2006), the analgesic codeine (Zanger et al., 2004), and the COX-2 inhibitor

celecoxib (Werner et al., 2003). It is important, therefore, that physicians are aware of the potential for clinically relevant interactions when prescribing antidepressants.

Desvenlafaxine is the major active metabolite of the serotonin-norepinephrine reuptake inhibitor venlafaxine; the free base of desvenlafaxine is also referred to as O-desmethylvenlafaxine (ODV). It is administered clinically as the succinate salt. Desvenlafaxine has been shown to selectively inhibit the reuptake of serotonin and norepinephrine (Deecher et al., 2006). Desvenlafaxine was recently approved for the treatment of major depressive disorder (MDD) and is currently in clinical development for other indications. (Wyeth Pharmaceuticals, 2008; Wyeth Pharmaceuticals, 2007) The biotransformation of venlafaxine to desvenlafaxine is primarily dependent on the CYP2D6 enzyme system (Shams et al., 2006); over 55% of an oral dose is recovered as desvenlafaxine and its glucuronide conjugate in the urine within 48 hours postadministration (Howell et al., 1993; Otton et al., 1996). However, desvenlafaxine is mainly eliminated unchanged by renal excretion, and to a lesser extent metabolized by phase II enzymes to form a glucuronide conjugate (Parker et al., 2005; Wyeth Pharmaceuticals, 2008). A small percentage of desvenlafaxine (<5%) is metabolized by CYP3A4 to form N,O-didesmethylvenlafaxine (Parker et al., 2005; Wyeth Pharmaceuticals, 2008) (Data on file).

In in vitro studies, no inhibition by desvenlafaxine of the CYP2D6 enzyme has been detected (K_i>300μM). In 2 previous studies designed to examine the effect of desvenlafaxine (100 and 400 mg) on the pharmacokinetics of the CYP2D6 probe desipramine, desvenlafaxine minimally decreased the clearance of a single 50-mg dose of desipramine (ie, an increase in the area under the plasma concentration-versus-time curve [AUC] of 17% and 90%, respectively) (Data on

file). Additionally, in a study using a similar design as the current study but with paroxetine (20 mg) as the active comparator, the AUC of desipramine when coadministered with paroxetine was 5 times that when desipramine was administered alone (Data on file).

The objective of the current study was to evaluate the effects of multiple doses of desvenlafaxine or duloxetine on the pharmacokinetics of single-dose desipramine in healthy subjects. Desipramine is primarily eliminated through CYP2D6-mediated metabolism by forming 2-hydroxydesipramine (Bjornsson et al., 2003); approximately 40% of a single, oral dose of desipramine is recovered as 2-hydroxydesipramine in the urine (Spina et al., 1996). A 50-mg dose of desipramine has been established as an appropriate substrate to test CYP2D6 inhibition (Preskorn and Flockhart, 2004; Preskorn et al., 1994). Duloxetine, a CYP2D6 inhibitor with an in vitro K_i of 4.5μM (Data on file), was included in this study as a positive control because it is a moderate inhibitor. Specifically, duloxetine (60 mg BID), administered with a single 50-mg dose of desipramine, has been shown to produce a 3-fold increase in the AUC of desipramine (Skinner et al., 2003).

METHODS

This single-center, randomized, open-label, 4-period crossover study was designed to evaluate the effects of multiple doses of desvenlafaxine (100 mg/d) and duloxetine (30 mg BID) on the pharmacokinetics of a single 50-mg dose of desipramine. Eligible subjects were admitted to an inpatient setting for up to 30 days between September 3, 2006 and October 3, 2006 in Neptune, New Jersey, maintained on a medium-fat diet throughout the study period, and received study medication at predetermined time points. Subjects were randomly assigned in a 1:1 ratio to treatment sequence A (desvenlafaxine/duloxetine) or B (duloxetine/desvenlafaxine).

Inclusion Criteria

Healthy men or women 18 to 55 years of age with a body mass index ranging from 18 kg/m^2 to 30 kg/m^2 and body weight ≥50 kg were enrolled. Women of childbearing potential were required to be nonlactating and not pregnant. If they were not either surgically sterile or postmenopausal, they had to be using an acceptable method of contraception, excluding hormonal therapy.

Exclusion Criteria

Subjects were excluded from the study under the following conditions: a history or current diagnosis of any disorder that might prevent successful completion of the study; a surgical or medical condition that might interfere with pharmacokinetic parameters; clinically significant abnormalities on 12-lead electrocardiogram (ECG) tracings; a PR interval >0.22 seconds, QRS complex >0.11 seconds, or QT/QT interval corrected for heart rate intervals >0.45 seconds; an acute disease within 7 days; known or suspected alcohol or other substance abuse; a history of

seizure; history of positive serology for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or HIV; recent blood or plasma donation; a history of clinically important allergy or reactions to desvenlafaxine, venlafaxine, duloxetine, desipramine, or imipramine; cigarette smoking in the last year; and use of hormonal therapy, investigational or prescription drugs within 30 days, tobacco or consumed caffeine- or grapefruit-containing products or alcohol within 48 hours, over-the-counter drugs including herbal supplements (except for acetaminophen and vitamins) within 14 days, or medroxyprogesterone (Depo-Provera®) within 90 days.

Study Design

At the screening visit, subjects provided written informed consent and a complete medical history. The following procedures were performed to ascertain the prospective subject's eligibility for participation: physical examination; vital signs; 12-lead ECG; laboratory evaluation, including HBsAg, HCV antibody, and HIV antibody screen; serum beta-human chorionic gonadotropin (in female subjects), and a urine drug and alcohol screening; inclusion/exclusion criteria review; demographic data collection; and a record of prior and concomitant medications.

During the first study period subjects were administered an initial dose of desipramine (day 1) followed by 120 hours of blood sample collection for pharmacokinetic analyses. Subjects were assessed daily on their use of concomitant medications, vital signs, and occurrence of adverse events (AEs) from day 1 until the end of the study. Blood sample collection for laboratory evaluation was conducted on study day 5. During period 2 (days 6-15) subjects received either

desvenlafaxine or duloxetine with 240 mL of room-temperature water within 5 minutes after breakfast. To allow test articles to reach steady-state concentrations prior to desipramine administration, subjects received desipramine on day 11, followed by 120 hours of blood sample collection for pharmacokinetic analyses. Period 3 (days 16-19) was a washout period. Period 4 (days 20-29) was the crossover phase of the study, when doses of the alternate agent from period 2 were administered daily with coadministration of desipramine occurring on day 25 (Fig. 1). Blood samples for pharmacokinetic analyses were again collected for up to 120 hours. Patients were discharged from the study on day 30. On the final day a physical examination was conducted, blood samples were collected for laboratory evaluations and pharmacokinetic analyses, and an assessment of vital signs, use of concomitant medications and AEs was performed.

All subjects were required to fast overnight for ≥10 hours before each desipramine administration and first blood sample collection. Blood samples (5 mL) were collected from an indwelling catheter or by direct venipuncture in sodium heparin-treated blood collection tubes and immediately placed on ice or refrigerated. Samples were centrifuged within 50 minutes after collection at 4°C and 2500 rpm (approximately 1000 g) for 15 minutes. Samples were stored frozen in an upright position at approximately –20°C until being shipped for bioanalysis.

Samples were collected for determination of desipramine and 2-hydroxydesipramine concentrations on study days 1 to 6, 11 to 16, and 25 to 30 within 2 hours before and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after desipramine administration. On days 11, 12, 25, and 26, blood samples were collected to measure steady-state trough desvenlafaxine and

duloxetine plasma concentrations. Collection occurred 30 minutes prior to desipramine administration on days 11 and 25, and at similar times on days 12 and 26.

Safety was evaluated using observed and spontaneously reported signs and symptoms, scheduled physical examinations, clinical laboratory evaluations, vital sign measurements, and 12-lead ECGs. AEs recorded throughout the study were coded using the Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary.

CYP2D6 Genotyping

Using blood collected on study day –1, CYP2D6 genotyping was performed by the Wyeth Biomarker Laboratory to ensure that changes in desipramine pharmacokinetics were the result of test agents rather than genetic predisposition to variations in drug metabolism. Whole blood samples were collected in K_3EDTA polypropylene tubes for the purpose of genomic DNA isolation and genotyping of single nucleotide polymorphisms. Samples were stored refrigerated in an upright position at 4°C until shipment. Genomic DNA was isolated from aliquots of all samples immediately upon arrival at the assessment site. All 20 whole blood samples analyzed in the present study yielded sufficient quantities of genomic DNA for CYP2D6 genotyping analysis.

For analysis of the CYP2D6*2, *3, *4, *6, *7, *8, *9, *17, *29, and *41 alleles, a CYP2D6-specific fragment was amplified by a nested PCR strategy and analyzed by primer extension and MALDI-TOF analysis using multiplexed methods developed and validated in the Wyeth Biomarker Laboratory (Wyeth Research, Collegeville, PA). Detection of the CYP2D6*10 allele was performed using a commercially available TaqMan allelic discrimination assay

(ABI, Foster City, CA) according to the manufacturer's instructions. Duplication (*xN) and deletion (*5) of the CYP2D6 gene were determined using the commercially available CYP2D6 Deletion/Duplication Polymerase Chain Reaction (PCR) Assay Kit (JuriLab, Finland) multiplex long PCR-based assay according to the manufacturer's instructions.

Genotype call acceptance criteria using the various technologies were assigned according to the methods outlined in Isler et al (Isler et al., 2007). During each analytical run of clinical samples for a given allele, both positive and negative controls, where available, were analyzed. Positive controls were human genomic DNA samples confirmed by direct dideoxy sequencing to be heterozygous or homozygous for the CYP2D6 allele of interest during method validation studies. Negative controls were human genomic DNA samples confirmed by direct sequencing to lack the CYP2D6 allele of interest.

Any subjects bearing either *1 or *2 in combination with a duplication of the CYP2D6 gene (*1xN or *2xN, respectively) were assigned ultra-rapid metabolizer status. Subjects with allele combinations possessing at least 1 functional allele (*1 or *2) in the absence of gene duplication resulted in an extensive metabolizer phenotype prediction. Subjects possessing 2 decreased activity alleles (*9, *10, *17, *29, and *41) or 1 decreased activity allele in combination with a null allele (*3, *4, *5, *6, *7, and *8) were assigned intermediate metabolizer status. Finally, subjects possessing a combination of 2 null alleles resulted in a poor metabolizer phenotype prediction. In this study, subjects who were not predicted to have an extensive metabolizer phenotype were excluded from the sensitivity analysis.

Analytic Methods

Desvenlafaxine

To determine the plasma concentrations of desvenlafaxine in the study samples, a validated method employing API 3000 liquid chromatography/tandem mass spectrometry (LC/MS/MS) was performed by BA Research International using nadolol as an internal standard. Nine different standard concentrations were used for the calibration curve; the curve was linear, with an r^2 value of 0.999536. The interface used with the LC/MS/MS was a Turbo Ionspray®. The positive ions were measured in multiple reaction monitoring mode. The LC flow rate was 0.400 mL/minute (±30%).

A protein precipitation extraction procedure was used. The analytical procedure involved the addition of 20.0 μL of deionized water to each 200 μL portion of standard solution and quality control (QC) sample, and 20.0 μL of 50% methanol-water solution to each 200 μL part of the study sample. To this mixture, 500 μL of working internal standard solution was added. After vortexing and centrifuging, 200 μL of the supernatant was transferred to an autoinjector vial. Following the addition of 1000 μL of dilution solution to each vial, 5.00 μL was injected into the LC/MS/MS system.

Data were acquired by and integrated on Applied Biosystems "Analyst" v. 1.4.1 software, and a linear regression with $1/x^2$ weighting was performed in Thermo Electron Corporation Watson LIMS version 6.4.0.02™ for Windows to obtain the best fit of the data for the calibration curves. The lower limit of quantitation was established at 2.000 ng/mL and the upper limit of quantitation was 500.0 ng/mL. The interday precision for the QC of the assessment could not

be calculated because the n was less than 3. The accuracy ranged from 100% to 104%. The QC samples met all acceptance criteria.

Duloxetine

To determine the plasma concentrations of duloxetine in the study samples, a validated method employing API 3000 liquid chromatography/tandem mass spectrometry (LC/MS/MS) was performed by BA Research International using fluoxetine as an internal standard. Nine different standard concentrations were used for the calibration curve; the curve was linear, with an r^2 value of 0.998158. The interface used with the LC/MS/MS was a Turbo Ionspray®. The positive ions were measured in multiple reaction monitoring mode. The LC flow rate was 0.450 mL/minute (±30%).

A protein precipitation extraction procedure was used. The analytical procedure involved the addition of 20.0 μL of deionized water to each 200 μL portion of standard solution and quality control (QC) sample, and 20.0 μL of 50% methanol-water solution to each 200 μL part of the study sample. To this mixture, 500 μL of working internal standard solution was added. After vortexing and centrifuging, 500 μL of mobile phase was transferred to an autoinjector vial. Following the addition of 1000 μL of dilution solution to each vial, 5.00 μL was injected into the LC/MS/MS system.

Data were acquired by and integrated on Applied Biosystems “Analyst” v. 1.4.1 software, and a linear regression with $1/x^2$ weighting was performed in Thermo Electron Corporation Watson LIMS version 6.4.0.02™ for Windows to obtain the best fit of the data for the calibration

curves. The lower limit of quantitation was established at 0.2000 ng/mL and the upper limit of quantitation was 50.00 ng/mL. The interday precision for the QC samples was 5.8% or better and the accuracy ranged from 98.6% to 107%. The QC samples met all acceptance criteria.

Desipramine and 2-hydroxdesipramine

Desipramine and 2-hydroxydesipramine plasma concentrations were assessed with a validated high-performance LC/MS/MS detection method using desipramine-d_3 hydrochloride and 2-hydroxydesipramine-d_3 hydrochloride as internal standards. The analytes were isolated from a 100-µL aliquot of human plasma by liquid-liquid extraction into a mixture of isopropanol / hexane / methyl t-butyl ether (5:47.5:47.5, v/v/v). The organic phase was separated, evaporated to dryness, and the residue was reconstituted in 500 μL of methanol / water (50:50, v/v).

Aliquots of the sample extracts (25 μL) were analyzed on a Sciex API 3000 LC/MS/MS system with a Turbo Ionspray® interface operated in positive ion mode. The analytes were chromatographically separated from endogenous matrix components using a BDS Hypersil C18, 2 mm x 50 mm, 3 µm, column with an isocratic mobile phase consisting of 2.0 mM ammonium formate, pH 3.0 / acetonitrile (20:80, v/v) at a flow rate of 0.200 mL/minute, and were detected by multiple reaction monitoring. This method was applicable to the quantitation of desipramine and 2-hydroxydesipramine within a nominal range of 0.250 to 100 ng/mL, using nine calibration standard levels. A linear, 1/concentration squared weighted, least-squares regression algorithm was used to obtain the best fit to the calibration curve. During the validation, the calibration curves for desipramine and 2-hydroxydesipramine had average correlation coefficients of 0.9995 and 0.9974, respectively. The intra- and inter-day precision

(%CV) for desipramine quality controls ranged from 2.6% to 8.2%, with mean differences from theoretical values ranging from –5.3% to –2.3%. The corresponding precision for 2-hydroxydesipramine ranged from 2.8% to 9.2%, with differences from theoretical values between –3.5% to 1.2%.

Pharmacokinetic and Statistical Analysis

A noncompartmental pharmacokinetic method was used to analyze the plasma concentrations of desipramine and 2-hydroxydesipramine. Peak plasma concentration (C_{max}) and time to peak concentration (t_{max}) were determined directly from observed data, and AUC, apparent terminal half-life ($t_{1/2}$), apparent oral-dose clearance (Cl/F; desipramine only), and apparent volume of distribution (desipramine only) were computed.

Summary statistics were provided for each treatment group. Hypothesis testing was performed at the 5% significance level. To assess the treatment effects on AUC and C_{max} between desvenlafaxine and duloxetine, a 2-period crossover analysis of variance on the logarithms ratio for the pharmacokinetic parameters (AUC and C_{max}) on each combined therapy to desipramine alone was performed. The geometric least square mean ratio and 90% confidence interval were reported.

RESULTS

Of the 47 individuals that were initially screened, 20 subjects were enrolled (4 subjects withdrew and 13 were declined because enrollment had been completed) Subjects had a mean age of approximately 35 years and were primarily male (80%); 45% were black and 30% were

Caucasian. There were no statistically significant differences in the demographic and baseline characteristics for the 2 treatment sequence groups. No subjects received concomitant therapy during the evaluation period. Four (20%) subjects, 2 from each sequence group, withdrew from the study prior to completion; 3 subjects receiving desvenlafaxine withdrew because of AEs and 1 subject receiving duloxetine requested withdrawal.

Pharmacokinetic Results

All subjects were included in the pharmacokinetic analysis. The mean predose concentrations of desvenlafaxine as assessed on days 11 and 12 were 166.96 ng/mL and 201.36 ng/mL, respectively, and 200.50 ng/mL and 207.04 ng/mL on days 25 and 26, respectively. The mean predose concentrations of duloxetine on days 11 and 12 were 35.85 ng/mL and 38.34 ng/mL, respectively, and 32.36 ng/mL and 34.57 ng/mL on days 25 and 26, respectively. These data are consistent with desvenlafaxine and duloxetine plasma concentrations reaching steady state after 5 days of dosing. The desvenlafaxine levels are similar to levels seen in other multiple-dose studies in which steady-state had been achieved (Data on file). There were no significant carry-over effects; therefore summary results are presented by combining across 2 periods for each treatment group.

Desipramine

The mean desipramine C_{max}, AUC, Cl/F, and $t_{1/2}$ were affected by the concomitant administration of desipramine with desvenlafaxine or duloxetine, but t_{max} was not affected (**Table 1**; **Figures 2** and **3**). According to the ratio of least square geometric (LSG) means, the C_{max} for desipramine was significantly greater after administration of duloxetine than

desvenlafaxine (63% vs 19%; P<0.001). The increase in LSG mean of AUC for desipramine was also significantly greater after duloxetine administration than after desvenlafaxine (122% vs 22%; P<0.001) (**Table 2**). The mean Cl/F for desipramine administered alone was 1.5 L/h/kg, but when combined with desvenlafaxine or duloxetine this value decreased to 1.2 L/h/kg and 0.6 L/h/kg, respectively. In addition, mean $t_{1/2}$ with desipramine alone was 18.9 h, which increased to 21.3 h with administration of desvenlafaxine and to 28.6 h with duloxetine.

2-hydroxydesipramine

The 2-hydroxydesipramine pharmacokinetic parameters were also affected by administration of desipramine in combination with desvenlafaxine and duloxetine (**Table 1**; **Figures 4** and **5**). Compared with desipramine alone, the change in LSG mean of the C_{max} for 2-hydroxydesipramine was significantly different with duloxetine coadministration compared with desvenlafaxine coadministration (–24% vs 9%; P<0.001) (**Table 2**). The LSG mean of AUC for 2-hydroxydesipramine increased similarly after coadministration of desipramine with desvenlafaxine or duloxetine (19% vs 26%; P=0.054) (**Table 2**). When compared with desipramine administered alone, both $t_{1/2}$ (20.4 h) and t_{max} (3.0 h) were affected to a greater extent with duloxetine (32.1 h and 11.9 h, respectively) than with desvenlafaxine (21.5 h and 7.0 h, respectively).

Eighteen (90%) subjects were predicted (based on genotype) to have an extensive metabolizer phenotype. Two subjects were excluded from the sensitivity analysis because 1 subject was predicted to have an intermediate metabolizer phenotype and another was predicted to have an

ultrarapid metabolizer phenotype. The results of the sensitivity analysis were consistent with those of the primary analysis.

Safety Analysis

All 20 subjects were included in the safety analysis, although 2 subjects withdrew before crossover. Seventeen subjects received desvenlafaxine and 17 received duloxetine; all 20 received at least 1 dose of desipramine. AEs occurred in 14 (70%) subjects overall. Nine of the 17 subjects (53%) receiving desvenlafaxine experienced an AE, as did 11 of the 17 subjects (65%) receiving duloxetine (**Table 3**). Headache was the most common AE with both desvenlafaxine and duloxetine (24% and 35%, respectively); diarrhea also frequently occurred with duloxetine (24%).

There was 1 serious AE reported: a 23-year-old man had a seizure on the second day of desvenlafaxine administration. The subject was withdrawn from the study and hospitalized for 1 day for further evaluation. A computed tomography scan did not indicate any intracranial processes or evident disorder. The subject remained asymptomatic during hospitalization and stabilized. There were 2 additional safety-related discontinuations. One subject experienced hypertension and tachycardia on the first day of desvenlafaxine administration (study day 6), while another experienced tachycardia on the first day of desvenlafaxine administration (study day 12).

Six subjects (30%) had potentially clinically important (PCI) changes in vital signs during the study. Two subjects (10%) had both a PCI increase and a PCI decrease in systolic blood

pressure. A PCI decrease in diastolic blood pressure, a PCI increase in diastolic blood pressure that was also elevated over 3 consecutive visits, and a PCI increase in pulse rate were each experienced by 2 study subjects. In addition, laboratory changes considered to be potentially clinically relevant occurred in 5 (25%) subjects overall. Hematuria and ketonuria were the most frequent PCI laboratory results (20% and 15% of subjects, respectively). There were no significant differences between treatment sequence groups, individual treatment groups, or combined treatment groups in any changes in vital signs and laboratory findings

DISCUSSION

The objective of this study was to assess and quantify the effect of a 100-mg daily dose of desvenlafaxine, twice the recommended therapeutic dose for MDD in the US, on CYP2D6 metabolism in humans. Desipramine exposure, as measured by the ratio of least square geometric mean C_{max} and AUC, increased only slightly during coadministration of desipramine and desvenlafaxine. These results are consistent with the absence of inhibition of CYP2D6 in vitro (IC_{50} > 100μM) and with what has been observed in a similarly-designed study conducted with desvenlafaxine (Data on file). However, in the current analysis a significantly greater increase in desipramine C_{max} and AUC was observed during coadministration of desipramine and duloxetine as compared to desipramine and desvenlafaxine. This finding was anticipated based on data from previously published reports with duloxetine (Preskorn et al., 2007a; Skinner et al., 2003). As expected, duloxetine caused an appreciable decrease in 2-hydroxydesipramine C_{max} when coadministered with desipramine. However, there was an unexpected modest increase in 2-hydroxydesipramine C_{max} with desvenlafaxine coadministration, and increases in 2-hydroxydesipramine AUC with desvenlafaxine or duloxetine coadminsistration; the reasons for these latter effects are unclear.

The safety and tolerability of desvenlafaxine in this study were consistent with what has been observed in clinical trials in depressed patients (Boyer et al., 2008; DeMartinis et al., 2007; Liebowitz et al., 2008) There was 1 serious AE reported in the study, a seizure followed by hypotension in a patient receiving desvenlafaxine; the patient remained asymptomatic and stable while hospitalized for 1 day following the event.

Although the current study population was comprised primarily of young men, these results are expected to be generalizable to other patient types. As poor metabolizers have only minimal CYP2D6 activity they are less likely to show the effects of CYP2D6 inhibition produced by compounds with inhibitory effects. Therefore the lack of poor metabolizers in the study population permitted observation of the more pronounced effects of CYP2D6 inhibition that can be observed in extensive metabolizers.

Clinical Considerations

Clinicians need to be aware of the potential for drug-drug interactions when prescribing CYP2D6-inhibiting antidepressants to patients receiving treatment for comorbid medical conditions. Nearly 25% of the drugs used in clinical practice are dependent on this hepatic enzyme for their metabolism (Ingelman-Sundberg, 2004). Patient groups that may be of particular concern include those being treated for breast cancer, and the elderly. In a study of approximately 2800 Veteran Affairs patients, 8% of the 461 patients receiving the CYP2D6-inhibiting antidepressants fluoxetine and/or paroxetine were also being treated with CYP2D6 substrates with a narrow therapeutic index. Thirty-six percent of these patients were being treated at doses high enough to have a moderate-to-high risk for drug-drug interactions (Preskorn et al., 2007c).

Inhibition of CYP2D6 activity has been shown to reduce the efficacy of tamoxifen, a selective estrogen receptor modulator used for the treatment and prevention of breast cancer. Tamoxifen is known to be dependent on CYP2D6 for biotransformation from its parent compound to an active metabolite (Goetz et al., 2007; Jin et al., 2005; Stearns et al., 2003; Goetz et al., 2005).

The minimal impact of desvenlafaxine on CYP2D6 activity may prove to be beneficial for this and other patient populations requiring concomitant treatment with agents dependent on CYP2D6.

The limitations of the current study (ie, the lack of real world outcomes in depressed patients and the predominantly male population) are outweighed by its strengths. These include the use of desipramine (an accepted and established CYP2D6 probe) in a single dose, which allowed for easier detection of pharmacokinetic changes. In addition, ensuring that desvenlafaxine and duloxetine reached steady-state concentrations prior to desipramine administration approximated the clinical circumstances of chronic treatment. Finally, the continued administration of test articles during the pharmacokinetic assessment period maximized the potential for detecting any inhibition.

The results of this study demonstrate that coadministration of the CYP2D6 substrate desipramine with 100-mg daily doses of desvenlafaxine, twice the recommended therapeutic dose for MDD in the US, resulted in exposure to desipramine and 2-hydroxydesipramine that was only slightly different than that observed when desipramine was administered alone. These data support prior findings suggesting that desvenlafaxine is not a substantial inhibitor of CYP2D6 activity (Preskorn et al., 2007b).

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Footnotes

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LEGENDS for FIGURES

1. Pharmacokinetic study flow

2. Mean desipramine plasma concentrations over time (combined treatment sequences)

3. Mean (± SD) desipramine AUC (ng·h/mL) (combined treatment sequences; n=20). Abbreviation: AUC, area under the plasma concentration-versus-time curve. *P<0.001, increase in desipramine concentration (relative to desipramine alone) observed with duloxetine/desipramine coadministration, compared to the increase observed with desvenlafaxine/desipramine coadministration.

4. Mean 2-hydroxydesipramine plasma concentrations over time (combined treatment sequences)

5. Mean (± SD) 2-hydroxydesipramine AUC (ng·h/mL) (combined treatment sequences; n=20). Abbreviation: AUC, area under the plasma concentration-versus-time curve. *P=0.054, increase in 2-hydroxydesipramine concentration (relative to desipramine alone) observed with duloxetine/desipramine coadministration, compared with the increase observed with desvenlafaxine/desipramine coadministration.

Table 1. Summary of pharmacokinetic parameters (plasma) for desipramine and 2-hydroxydesipramine (for both treatment patterns combined; n=20)

Assessment	**C_{max}, ng/mL**		**t_{max}, h**	**AUC, ng*h/mL**		**$t_{1/2}$, h**		**Cl/F, L/h/kg**	
Treatment	Geometric Mean	Arithmetic Mean (SD)	Median (range)	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)
Desipramine									
Desipramine 50 mg	14.7	16.1 (6.2)	8.0 (4.0–16.0)	428	516 (301)	18.9	20.0 (7.1)	1.5	1.8 (1.5)
Desipramine 50 mg + desvenlafaxine 100 mg QD	17.8	18.6 (5.5)	8.0 (6.0–16.0)	528	594 (298)	21.3	22.2 (6.4)	1.2	1.3 (0.7)
Desipramine 50 mg + duloxetine 30 mg BID	24.7	25.8 (7.9)	8.0 (6.0–16.0)	995	1069 (399)	28.6	29.4 (7.0)	0.6	0.7 (0.3)
2-hydroxydesipramine									
Desipramine 50 mg	11.9	12.6 (4.1)	3.0 (2.0–16.0)	336	343 (69)	20.4	21.5 (7.7)	-	-
Desipramine 50 mg + desvenlafaxine 100 mg QD	13.2	13.9 (4.5)	7.0 (2.0–16.0)	403	410 (75)	21.5	22.2 (6.3)	-	-
Desipramine 50 mg + duloxetine 30 mg BID	8.9	9.5 (3.2)	11.9 (2.0–16.0)	430	437 (79)	32.1	33.9 (12.9)	-	-

Abbreviations: AUC, area under the plasma concentration-versus-time curve; BID, twice daily; Cl/F, apparent oral-dose clearance; C_{max}, peak plasma concentration; QD, once daily; t_{max}, time to peak concentration; $t_{1/2}$, apparent terminal-phase elimination half-life.

Table 2. Effects of combination treatment[a] on desipramine pharmacokinetic parameters: LSG mean ratio[b] (90% confidence limits)

	Desipramine		**2-hydroxydesipramine**	
	AUC (ng*h/mL)	**C_{max} (ng/mL)**	**AUC (ng*h/mL)**	**C_{max} (ng/mL)**
Treatment				
Desipramine + desvenlafaxine 100 mg QD	122% (107%, 138%)	119% (108%, 130%)	119% (114%, 125%)	109% (100%, 119%)
Desipramine + duloxetine 30 mg BID	222% (195%, 251%)	163% (149%, 179%)	126% (120%, 132%)	76% (71%, 83%)
P value[c]	< 0.001	< 0.001	0.054	< 0.001

Abbreviations: ANOVA, analysis of variance; AUC, area under the plasma concentration-versus-time curve; BID, twice daily; C_{max}, peak plasma concentration; LSG, least square geometric; QD, once daily.
[a]Pooled treatments from different periods.
[b]Ratio to desipramine alone.
[c]*P* values based on comparison of desipramine + desvenlafaxine versus desipramine + duloxetine using a 2-period crossover ANOVA of LSG mean ratios.

Table 3. Treatment-emergent AEs that occurred in 2 or more subjects in any group, safety population, n (%)

Body System AE	Desipramine/ Desvenlafaxine (n=16)	Desvenlafaxine 100 mg (n=17)	Desipramine/ Duloxetine (n=17)	Duloxetine 30 mg (n=17)	Desipramine (n=20)
Any AE	3 (19)	9 (53)	6 (35)	11 (65)	2 (10)
Body as a Whole					
Headache	2 (13)	4 (24)	1 (6)	6 (35)	0
Cardiovascular					
Tachycardia	0	0	2 (12)	0	1 (5)
Digestive					
Anorexia	0	0	0	2 (12)	0
Diarrhea	0	1 (6)	0	4 (24)	0
Dry mouth	0	1 (6)	2 (12)	1 (6)	1 (5)
Nausea	0	1 (6)	0	2 (12)	0
Nervous					
Dizziness	0	2 (12)	0	1 (6)	0

Abbreviation: AE, adverse event.

Figure 1.

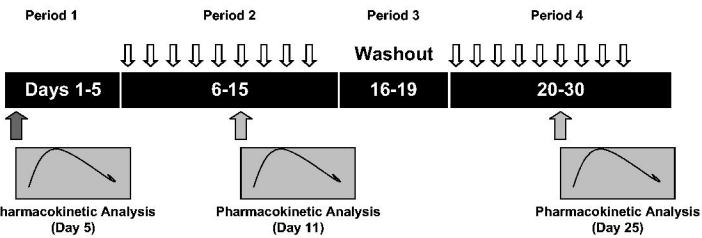

Period 1
Period 2
Period 3
Period 4
Washout
Days 1-5
6-15
16-19
20-30
Pharmacokinetic Analysis (Day 5)
Pharmacokinetic Analysis (Day 11)
Pharmacokinetic Analysis (Day 25)
Single dose desipramine 50 mg followed by 120 hour blood sampling for pharmacokinetic evaluation
Desvenlafaxine 100 mg QD or duloxetine 30 mg BID
Single dose desipramine 50 mg coadministered with desvenlafaxine 100 mg or duloxetine 30 mg BID, followed by 120 hours of pharmacokinetic determination

Figure 2.

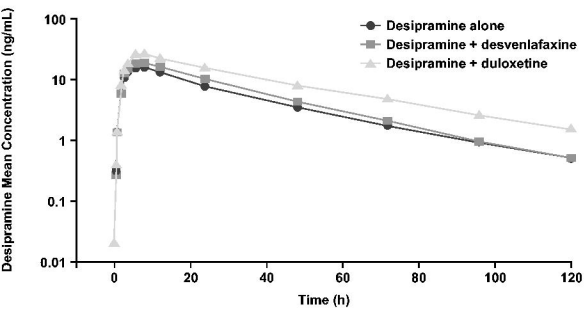

Desipramine alone
Desipramine + desvenlafaxine
Desipramine + duloxetine
Desipramine Mean Concentration (ng/mL)
100
10
1
0.1
0.01
0
20
40
60
80
100
120
Time (h)

Figure 3.

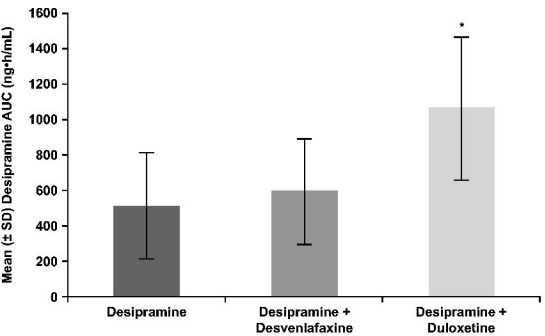

Mean (± SD) Desipramine AUC (ng•h/mL)
1600
1400
1200
1000
800
600
400
200
0
*
Desipramine
Desipramine + Desvenlafaxine
Desipramine + Duloxetine

Figure 4.

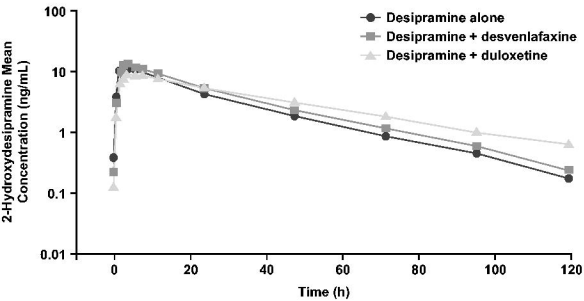
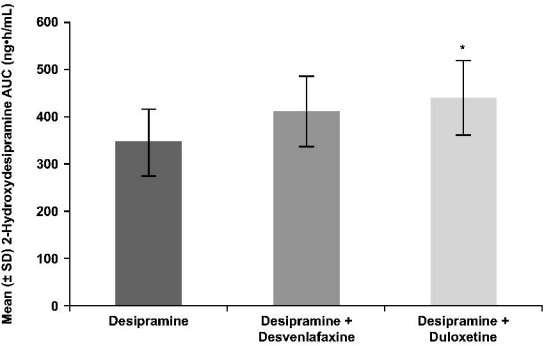

Desipramine alone
Desipramine + desvenlafaxine
Desipramine + duloxetine
2-Hydroxydesipramine Mean Concentration (ng/mL)
100
10
1
0.1
0.01
0
20
40
60
80
100
120
Time (h)

Figure 5.


Mean (± SD) 2-Hydroxydesipramine AUC (ng•h/mL)
600
500
400
300
200
100
0
*
Desipramine
Desipramine + Desvenlafaxine
Desipramine + Duloxetine