Venlafaxine in Human Breast Milk and Nursing Infant Plasma: Determination of Exposure

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Objective: Venlafaxine use during pregnancy has increased over the past decade in concert with accumulating reproductive safety data; however, systematic data on venlafaxine during lactation remain sparse. The current study characterizes the level and determinants of venlafaxine and desvenlafaxine concentrations in breast milk and in nursing infant plasma.

Method: Women participating in a prospective investigation of perinatal pharmacokinetics from January 2001 through July 2006 who were treated with venlafaxine and who chose to continue venlafaxine during lactation were included in the analysis. Breast milk samples were collected via breast pump from foremilk to hindmilk from a single breast to determine the excretion gradient, and serial samples were collected over 24 hours to determine the time course of excretion. Paired maternal/infant plasma samples were also collected. Venlafaxine and desvenlafaxine concentrations were determined using high-performance liquid chromatography with ultraviolet detection. Statistical analyses of breast milk and infant plasma concentrations and their determinants were conducted.

Results: Thirteen women and their nursing infants participated, providing 106 breast milk samples. The mean milk/plasma ratio was 275.3% (95% CI = 144.8% to 405.7%). There were statistically significant time courses of excretion for venlafaxine ($R = 0.36$, $F = 6.82$, $P < .02$), desvenlafaxine ($R = 0.48$, $F = 4.41$, $P < .009$), and combined venlafaxine/desvenlafaxine ($R = 0.51$, $F = 5.16$, $P < .004$), with the highest venlafaxine and desvenlafaxine concentrations in the breast milk occurring 8 hours after maternal ingestion. Infant plasma concentrations for combined venlafaxine/desvenlafaxine were 37.1% of maternal plasma concentrations. The theoretical infant venlafaxine/desvenlafaxine dose was 0.208 mg/kg/d, and the relative infant venlafaxine/desvenlafaxine dose was 8.1%. The theoretical and relative infant doses for desvenlafaxine were 197% and 224% higher, respectively, than those for venlafaxine. No adverse events were observed or reported in the nursing infants.

Conclusions: Consistent with previous investigations of medications in breast milk, the venlafaxine and desvenlafaxine milk/plasma ratios were highly variable. The rate of venlafaxine/desvenlafaxine excretion into human breast milk is relatively higher than that observed for other antidepressants, largely due to higher desvenlafaxine excretion. These data expand the extant literature on venlafaxine and desvenlafaxine in lactation.

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Breast-feeding has garnered global recognition by virtually all professional organizations as the ideal source of infant nutrition.[1] Consequently, both the proportion of women choosing to breast-feed[2] and the duration of lactation[3] have steadily increased. Decisions regarding breast-feeding, however, may be complicated by the occurrence of postpartum maternal mental illness and/or the continuation of psychotropic medications utilized during pregnancy.[4] Prescribing medications to lactating women represents a clinical conundrum in which the risks of infant medication exposure must be weighed against the benefits of lactation.

Venlafaxine was the first nontricyclic, dual serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant approved for use in the United States. Venlafaxine subsequently obtained US Food and Drug Administration approval for generalized anxiety disorder and social anxiety disorder and is frequently used off-label for other psychiatric and neurologic disorders. Furthermore, its active metabolite desvenlafaxine was recently approved for the treatment of major depressive disorder (MDD). It has been suggested that SNRI antidepressants may provide superior efficacy in achieving full remission from MDD; this issue continues to be debated.[5]

To date, the published data regarding venlafaxine and lactation include 5 reports[6–10] collectively encompassing 16 mother-infant nursing pairs. Three of these reports[6–8] are of maternal and nursing infant plasma concentrations of venlafaxine/desvenlafaxine combined with serial assessments of venlafaxine/desvenlafaxine breast milk concentrations in

a total of 13 mother-infant dyads; however, only 2 of these 3 studies used serial milk samples to analyze the time course of venlafaxine/desvenlafaxine excretion.[6,7] Other publications include a report of a single spot breast milk sample[9] and a report of paired maternal-infant plasma concentrations without breast milk sampling in 2 nursing dyads.[10] Across these studies, no pattern of potential adverse effects has been reported. The current study sought to extend the limited extant data, characterizing the levels and determinants of venlafaxine and desvenlafaxine concentrations in breast milk and nursing infant plasma.

METHOD

Women referred to the Emory Women's Mental Health Program during pregnancy were recruited into a prospective observational study of the perinatal course of neuropsychiatric illness and the pharmacokinetics of neuropsychiatric medications during pregnancy and lactation. Women participating from January 2001 through July 2006 who chose to breast-feed during treatment with venlafaxine were eligible for the current analysis. Subjects were informed of the available safety data regarding infant exposure to venlafaxine during lactation and the potential risks of untreated maternal mental illness. In addition, the risks and benefits of alternative treatments were reviewed. Inclusion criteria for the current analysis included (1) ≥ 18 years of age and able to provide informed consent, (2) on a stable maternal daily dose of venlafaxine for longer than 2 weeks, and (3) willing to collect breast milk samples and/or infant plasma (in addition to maternal plasma) for quantification of venlafaxine and desvenlafaxine concentrations. Infant plasma collection was requested but was not a requirement of study participation. Written informed consent was obtained prior to data collection. The Institutional Review Board of the Emory University School of Medicine approved the study.

Sample Collection

All plasma and breast milk samples were obtained after maternal plasma venlafaxine and desvenlafaxine concentrations would have achieved steady state (ie, > 5 elimination half-lives). Maternal plasma, infant plasma, and breast milk were collected as previously described in detail.[11–14] Briefly, breast milk samples were collected from the same breast using electric or manual breast pumps for time-course analysis (foremilk collected every 4 hours for 24 hours) and foremilk-to-hindmilk gradient analysis (10-mL aliquots from a single breast at a single time). The samples were coded and stored at −80°C until assay.

Determination of Venlafaxine and Desvenlafaxine Concentrations

Breast milk concentrations of venlafaxine and desvenlafaxine were determined using a mixed-bed solid-phase extraction followed by a high-performance liquid chromatography (HPLC) separation and ultraviolet detection method. Briefly, to a 1-mL sample of milk we added 100 µL of 12.5-µg/mL WY45818 (a venlafaxine analog) in 20% acetonitrile in water as internal standard. The sample was further diluted with 4 mL of water and 2 mL of 0.1M sodium phosphate buffer (pH 6.0). The diluted sample was mixed and then centrifuged at 1000*g* for 10 minutes. The supernatant was applied to a preconditioned Clean Screen extraction column (United Chemical Technologies, Bristol, Pennsylvania). The extraction cartridge was preconditioned with 3 mL of methanol, followed by 3 mL of water, followed by 1 mL of 0.1M sodium phosphate buffer (pH 6.0). The diluted sample was applied to the cartridge, and, after the sample was absorbed, the cartridge was washed with 3 mL of water, followed by 1 mL of 1M acetic acid. The cartridge was dried under vacuum for 5 minutes. The compounds of interest were eluted with 3 mL of a mixture of dichloromethane, isopropyl alcohol, and ammonia (proportions of 78/20/2, respectively). The elute was taken to dryness under a stream of nitrogen and reconstituted in 250 µL of HPLC mobile phase. One hundred microliters of sample was applied to the HPLC.

The HPLC system employed was similar to assay system 3 previously described by Hostetter et al.[15] The primary modification was an alteration of the mobile phase employed (19% acetonitrile, 81% 0.02M potassium phosphate buffer [pH 6.1] plus 15 µL/L N,N-dimethyloctylamine). The HPLC output was monitored at 225 nm. A 5-point standard curve was used in each assay run, and 2 levels of quality control samples were analyzed in duplicate in each assay run. The limit of detection for the assay is 0.5 ng/mL, and the limit of quantitation is 2 ng/mL for both compounds. The procedure is linear to 500 ng/mL for both compounds. The intra-assay coefficient of variation was 2% for venlafaxine and 5% for desvenlafaxine at both 100 ng/mL and 350 ng/mL. The interassay variation was 12% for venlafaxine and 13% for desvenlafaxine at both 100 ng/mL and 350 ng/mL over 10 assays. Matrix effects were assessed by spiking 5 different drug-free breast milk samples (from different donors). Recoveries for venlafaxine and desvenlafaxine were 97% or higher for all samples.

Data Analysis

The stages of data analysis included (1) demographic analysis to characterize the study sample; (2) analysis of breast milk concentrations including characterization of the potential foremilk-to-hindmilk excretion gradient and the 24-hour time course of excretion; calculation of milk/plasma (M/P) ratios at the minimum, maximum, and mean breast milk concentrations for each participant; estimation of theoretical infant dose (TID); and estimation of the relative infant dose (RID); (3) assessment of the determinants of breast milk concentrations using univariate and multivariate analyses of maternal factors—maternal daily dose, maternal plasma concentrations, and time after maternal

dose; and (4) analysis of infant plasma concentrations including calculation of the infant-to-maternal plasma ratios for venlafaxine and desvenlafaxine.

Analysis of breast milk concentrations. To determine the foremilk-to-hindmilk excretion gradient, the concentration for each fraction was divided by that of the minimum observed breast milk (BM) concentration ($[BM_{min}]_{grad}$) and presented as a ratio for each 10-mL aliquot from foremilk to hindmilk. Linear regression was performed to characterize the foremilk-to-hindmilk excretion gradient curve. The time course of excretion was calculated in a similar fashion using the minimum breast milk concentration ($[BM_{min}]_{time}$) observed over a 24-hour period.

The combined concentrations of venlafaxine/desvenlafaxine in breast milk were divided by combined venlafaxine/desvenlafaxine in maternal plasma to provide the M/P ratio. Because each participant provided multiple breast milk samples (to complete the excretion and time course analyses), we were able to calculate M/P ratio not just for a single spot sample but for the minimum, maximum, and mean breast milk concentrations over a 24-hour period for each participant.

The TID, estimated in mg/kg/d, was calculated using the formula put forth by Atkinson et al[16] (TID = daily breast milk intake [150 mL/kg/d] × breast milk concentration of medication). Each subject's mean breast milk concentration was multiplied by 0.000001 (to convert the concentration units from ng/mL to mg/mL) and then multiplied by the estimated infant daily breast milk intake of 150 mL/kg/d. The RID, expressed as a percentage, was calculated by dividing the TID by the maternal daily dose (also reported in mg/kg/d, assuming an average maternal weight of 70 kg). The RID and TID were calculated for venlafaxine, desvenlafaxine, and combined venlafaxine/desvenlafaxine.

Determinants of breast milk concentrations. Pearson correlation coefficients were calculated in an initial univariate analysis of the maternal characteristics predicting breast milk concentration. Subsequently, multiple regression analysis was performed. Candidate predictors of breast milk venlafaxine and desvenlafaxine concentrations included maternal daily dose, maternal plasma concentrations of venlafaxine and desvenlafaxine, hours post–maternal dose when the breast milk sample was collected, and the sequential aliquot number for those samples collected as part of a foremilk-to-hindmilk gradient analysis. Raw data were normalized via logarithmic transformation, and a backward elimination procedure with $\alpha = .05$ for retention was used.

Analysis of infant plasma concentrations. Whereas breast milk concentrations can be used to derive TID and RID estimates of infant exposure during lactation, actual infant exposure may be better represented by infant plasma concentrations. Infant plasma to maternal plasma ratios of venlafaxine, desvenlafaxine, and combined venlafaxine/desvenlafaxine were calculated to provide an index of actual infant exposure relative to maternal exposure.

RESULTS

Demographic Analysis

Thirteen nursing mothers and their infants participated in the current study. Of these, 84.6% (n = 11) were white and 23.1% (n = 3) were of Hispanic descent. The percentage of married mothers was 92.3% (n = 12), and 7.7% (n = 1) were divorced. Mean age of the participants was 33.5 (95% CI = 31.1 to 35.8) years, and mean years of education were 16.2 (95% CI = 13.9 to 18.4) years.

Two (15.4%) of the nursing mothers were treated with immediate-release venlafaxine (subject A in Table 1 and subject AA in Table 2); the remaining 11 (84.6%) received extended-release venlafaxine therapy. One (7.7%) of the nursing mothers initiated venlafaxine therapy immediately after delivery (subject A in Table 1); the remaining 12 (92.3%) received venlafaxine treatment during pregnancy and the postpartum period. Three (23.1%) of the participants were receiving psychotropic cotherapy at the time of sampling (subject D in Table 1: trazodone 100 mg/d; subject H in Tables 1 and 2: quetiapine 75 mg/d; subject I in Table 1: buspirone 10 mg/d). Two (15.4%) of the participants were cigarette smokers at the time of sampling (subjects E and K in Table 1).

Infants in the current sample were generally healthy at delivery. All had 5-minute Apgar scores of 8 or higher. Only 1 infant (7.7%) was admitted to a neonatal intensive care unit (NICU). That child (subject F in Tables 1 and 2) stayed in the NICU 18 hours due to tachypnea, receiving oxygen via nasal cannula. Three infants (23.1%) were born slightly preterm (subject D in Table 1: at 36.1 weeks; subject H in Tables 1 and 2: at 36.3 weeks; and subject J in Tables 1 and 2: at 36.7 weeks). At the time of sampling, 2 (15.4%) of the infants were receiving approximately 50% of their oral intake via lactation (subject E in Table 1 and subject H in Tables 1 and 2); the remaining infants were exclusively breast-fed. No adverse events were identified among either the mothers or their nursing infants via maternal interview and review of pediatric records.

Three participants provided breast milk samples, maternal plasma samples, and infant plasma samples; 3 provided paired breast milk and maternal plasma samples; 5 provided breast milk samples only; and 2 provided paired infant/maternal plasma samples but no breast milk samples. One participant provided an infant plasma sample but no maternal plasma or breast milk sample. Collectively, the participants provided 106 breast milk samples, 8 maternal plasma samples, and 6 infant plasma samples. The breast milk samples included (1) 52 samples collected by 8 women for foremilk-to-hindmilk gradient analysis, (2) 48 samples collected by 8 women for 24-hour time-course analysis, and (3) 6 spot samples. The breast milk samples were collected at a mean of 20.1 (95% CI = 8.6 to 31.7) weeks postpartum at a mean maternal daily venlafaxine dose of 183.8 mg (95% CI = 125.2 to 242.3 mg).

Table 1. Venlafaxine and Desvenlafaxine Concentrations in Maternal Plasma and Breast Milk With Infant Dose Estimates[a]

Subject	Infant Age, wk	Maternal Dose, mg/d	Maternal Plasma Concentration, ng/mL		Breast Milk Concentration, ng/mL									Infant Daily Dose of Venlafaxine + Desvenlafaxine	
					Minimum			Maximum			Mean				
			Venlafaxine	Desvenlafaxine	Venlafaxine	Desvenlafaxine	M/P Ratio, %	Venlafaxine	Desvenlafaxine	M/P Ratio, %	Venlafaxine	Desvenlafaxine	M/P Ratio, %	Theoretical, mg/kg/d	Relative, %
A	…	37.5	…	…	89	133	…	268	422	…	156.0	318.0	…	0.071	13.3
B	15.4	112.5	83	209	97	558	224.3	173	666	287.3	123.0	616.2	253.1	0.111	6.9
C	13.3	150	…	…	25	553	…	234	1781	…	125.2	1306.3	…	0.215	10.0
D	14.9	150	…	…	56	414	…	252	2255	…	137.9	928.3	…	0.160	7.5
E	35.2	150	…	…	80	395	…	641	1846	…	204.6	903.4	…	0.166	7.8
F	15.6	187.5	211	170	405	243	170.1	2759	824	940.4	1191.0	512.7	447.1	0.256	9.5
G	6.4	225	…	…	104	1213	…	481	3146	…	193.6	1851.2	…	0.307	9.5
H	60.0	225	134	233	181	487	182.0	557	1048	437.3	375.7	692.8	291.1	0.160	5.0
I	10.9	300	…	…	297	1454	…	850	2514	…	584.7	1912.7	…	0.375	8.7
J	18.3	300	110	345	134	683	179.6	221	801	224.6	177.0	735.2	200.5	0.137	3.2
K	19.8	300	1003	207	1422	291	141.6	2407	363	228.9	1899.3	332.0	184.4	0.335	7.8
Group Results															
Mean	20.9	194.3	308.2	232.8	262.7	584.0	179.5	803.9	1424.2	423.7	469.8	919.0	275.3	0.208	8.1
95% CI	9.8 to 32.2	137.1 to 251.6	−177.7 to 794.1	150.1 to 315.5	−6.3 to 531.8	311.6 to 856.4	142.6 to 216.5	194.1 to 1413.8	796.0 to 2052.4	49.5 to 798.0	85.9 to 853.7	547.7 to 1290.2	144.8 to 405.7	0.143 to 0.274	6.3 to 9.9

[a]Subjects are listed in order of maternal dose.
Abbreviation: M/P Ratio = milk/plasma ratio for combined venlafaxine/desvenlafaxine concentrations.
Symbol: … = data not available.

Table 2. Infant-Maternal Paired Plasma Samples: Venlafaxine and Desvenlafaxine Concentrations and Ratios[a]

Subject[b]	Infant Age, wk	Infant Daily Dose[c]		Infant Plasma Concentration, ng/mL		Maternal Dose, mg/d	Maternal Plasma Concentration, ng/mL		Infant-Maternal Plasma Ratio, %		
		Theoretical, mg/kg/d	Relative, %	Venlafaxine	Desvenlafaxine		Venlafaxine	Desvenlafaxine	Venlafaxine	Desvenlafaxine	Venlafaxine + Desvenlafaxine
AA	7.3	…	…	<2	47	150	23	23	8.7	204.3	106.5
C	8.4	0.215	10.0	5	243	150	32	403	15.5	60.3	57.0
AB	12.0	…	…	<2	54	225	59	224	3.4	24.1	19.8
F	12.4	0.256	9.5	<2	4	187.5	…	…	…	…	…
J	18.3	0.137	3.2	<2	<2	300	110	345	1.8	0.6	0.9
H	60.0	0.160	5.0	<2	<2	225	134	233	1.5	0.9	1.1
Group Results											
Mean	19.7	0.192	6.9	2.5	58.7	206.3	71.6	245.6	6.2	58.0	37.1
95% CI	−1.4 to 40.8	0.106 to 0.278	1.6 to 12.3	1.2 to 3.8	−39.3 to 156.6	146.6 to 265.9	11.3 to 132.0	64.7 to 426.5	−1.2 to 13.6	−47.9 to 164.0	−18.9 to 93.0

[a]Subjects are sorted by infant age at time of sampling.
[b]Subjects who provided both breast milk samples and paired infant-maternal plasma samples are identified by the same letter in both Table 1 and Table 2. Subjects who provided plasma samples but not breast milk samples appear only in Table 2 and are identified by letters AA and AB.
[c]The estimates of infant daily dose of combined venlafaxine and desvenlafaxine were derived from breast milk data (Table 1) when available.
Symbol: … = data not available.

Analysis of breast milk concentrations. A statistically significant time course of excretion was observed for venlafaxine, desvenlafaxine, and combined venlafaxine/desvenlafaxine (Figure 1). The time course data for venlafaxine ($R = 0.36$, $F = 6.82$, $P < .02$), desvenlafaxine ($R = 0.48$, $F = 4.41$, $P < .009$), and combined venlafaxine/desvenlafaxine ($R = 0.51$, $F = 5.16$, $P < .004$) were each best fit by a third-order polynomial regression. There was no statistically significant foremilk-to-hindmilk excretion gradient pattern for venlafaxine, desvenlafaxine, or combined venlafaxine/desvenlafaxine (data not shown).

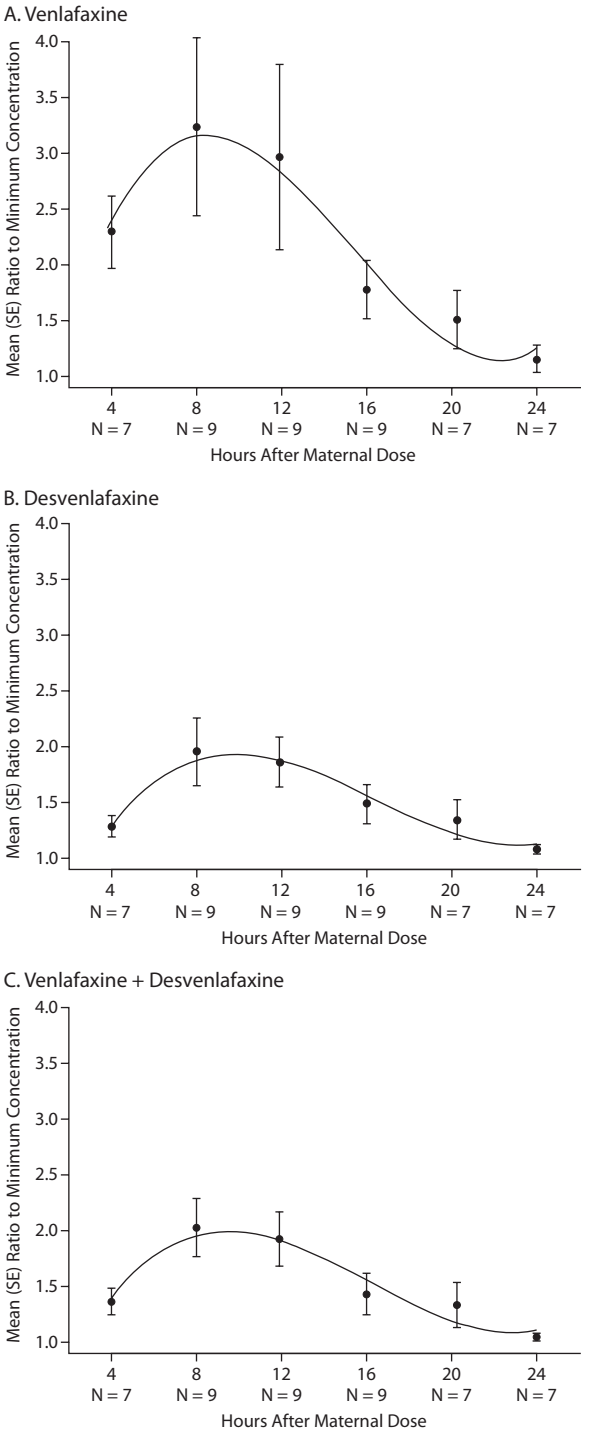
Milk/plasma ratios (Table 1) for combined venlafaxine/desvenlafaxine were high yet demonstrated wide variability ranging from a low of 141.6% at minimal breast milk concentrations to a peak of 940.4% at maximal breast milk concentrations. At the mean breast milk concentration for each participant, the M/P ratios were 275.3% (95% CI = 144.8% to 405.7%) for combined venlafaxine/desvenlafaxine, 268.7% (95% CI = 53.6% to 483.7%) for venlafaxine, and 253.4% (95% CI = 174.3% to 332.6%) for desvenlafaxine. Milk/plasma ratios for combined venlafaxine/desvenlafaxine equaled 179.5% (95% CI = 142.6% to 216.5%) when calculated using the minimum breast milk concentration for each participant and were 2.4 times higher at 423.7% (95% CI = 49.5% to 798.0%) when determined using the maximum breast milk concentration.

The mean breast milk concentrations for each individual were used to calculate the TID and RID. The TID for combined venlafaxine/desvenlafaxine was 0.208 mg/kg/d (95% CI = 0.143 to 0.274 mg/kg/d). The TID equaled 0.070 mg/kg/d (95% CI = 0.013 to 0.128 mg/kg/d) for venlafaxine and 0.138 mg/kg/d (95% CI = 0.082 to 0.194 mg/kg/d) for desvenlafaxine. The RID for combined venlafaxine/desvenlafaxine was 8.1% (95% CI = 6.3% to 9.9%). The RID for venlafaxine equaled 2.5% (95% CI = 0.9% to 4.0%) and for desvenlafaxine equaled 5.6% (95% CI = 3.8% to 7.4%).

Determinants of breast milk concentrations. Univariate Pearson correlation coefficients demonstrated that the breast milk venlafaxine concentration was positively correlated with the venlafaxine concentration in maternal plasma ($r = 0.94$, $P < .0001$) and with the maternal daily venlafaxine dose ($r = 0.33$, $P < .0007$) but was not correlated with maternal desvenlafaxine concentration, hours since last dose at time of sample collection, or weeks postpartum. Breast milk desvenlafaxine concentration was positively correlated with the desvenlafaxine concentration in maternal plasma ($r = 0.68$, $P < .0001$) and with maternal daily venlafaxine dose ($r = 0.27$, $P < .008$) but was negatively correlated with the venlafaxine concentration in maternal plasma ($r = -0.54$, $P < .0009$), weeks postpartum ($r = -0.36$, $P < .0002$), and the venlafaxine concentration in breast milk ($r = -0.24$, $P < .02$). Breast milk desvenlafaxine concentration was not correlated with the number of hours since the last maternal venlafaxine dose.

Analysis of infant plasma concentrations. Paired plasma samples were collected from 5 breast-feeding women and

Figure 1. Time Course of Excretion of (A) Venlafaxine, (B) Desvenlafaxine, and (C) Combined Venlafaxine/Desvenlafaxine Into Human Breast Milk[a]



[a]Mean ratio of venlafaxine, desvenlafaxine, and combined venlafaxine/desvenlafaxine concentration to the minimum breast milk concentration in each set of samples plotted by the number of hours after maternal ingestion of venlafaxine over a 24-hour window. The data shown represent 48 samples collected from 8 women. The time course of excretion data for venlafaxine ($R = 0.36$, $F = 6.82$, $P < .02$), desvenlafaxine ($R = 0.48$, $F = 4.41$, $P < .009$), and combined venlafaxine/desvenlafaxine ($R = 0.51$, $F = 5.16$, $P < .004$) were all best fit by a third-order polynomial regression.

their infants (Table 2). The infant-maternal ratio for venlafaxine equaled 6.2% (95% CI = −1.2% to 13.6%); however, the infant-maternal desvenlafaxine ratio was 9.4 times higher at 58.0% (95% CI = −47.9% to 164.0%).

DISCUSSION

There has been considerable debate regarding the relative safety of medications during lactation and the optimal means for quantifying the level and impact of nursing infant exposure, ie, M/P ratio, TID, RID, nursing infant plasma concentrations, and reported adverse events. The principal reference sources for information regarding medication use during lactation, ie, *Medications and Mothers' Milk*,[17] the American Academy of Pediatrics Committee on Drugs report,[18] and the National Library of Medicine's LactMed database,[19] rely on these parameters when assigning safety classifications for specific medications in lactation. The current investigation extends the previous literature by providing the largest and most detailed study of venlafaxine/desvenlafaxine excretion into human breast milk and presents results in the context of the parameters noted above.

Combined venlafaxine/desvenlafaxine concentrations in breast milk and M/P ratios were highly variable, ranging from 222 ng/mL to 3,627 ng/mL and from 141.6% to 940.4%, respectively. The considerable variability in these results demonstrates the imprecision and subsequent limited utility of M/P ratios derived from spot breast milk analysis as an estimate of exposure during lactation.

The mean RID in this sample (8.1% [95% CI = 6.3% to 9.9%]) was modestly higher than previously reported (3.5%–7.6%; collective n = 13).[6–9] This degree of disparity could readily be explained by inconsistent methods for collection and characterization of the breast milk samples from study to study, as suggested by the wide variation between maximum and minimum venlafaxine/desvenlafaxine in the current study (Table 1). Standard reference texts regarding medications and lactation suggest a 10% RID as an empirical cutoff for assuming medication safety during lactation.[17,20] Although the 8.1% RID for combined venlafaxine/desvenlafaxine falls within this de facto 10% guideline, clinicians should be advised that this rule of thumb is without objective verification of relevance for nursing infant safety.

It is noteworthy that excretion into breast milk was disproportionately higher for desvenlafaxine than for venlafaxine. The TID for desvenlafaxine was 197% higher than the TID for venlafaxine (0.138 mg/kg/d vs 0.070 mg/kg/d). Similarly, the RID for desvenlafaxine was 224% higher than the RID for venlafaxine (5.6% vs 2.5%). Moreover, the infant-to-maternal plasma ratio for desvenlafaxine was 935% higher than the infant-to-maternal plasma ratio for venlafaxine (58.0% vs 6.2%). These results contrast with the earlier reports by Ilett and colleagues[6,7] in which venlafaxine and desvenlafaxine were reported to contribute equally to the RID. However, the reliance on 12 hours of breast milk sampling in the Ilett et al[6,7] studies (rather than the 24-hour interval used in the current study) to produce the RID estimates may underestimate the relative contribution of desvenlafaxine excretion. Visual inspection of the time course data from both the current study (Figure 1) and the Ilett et al[6,7] reports indicates that breast milk concentrations of venlafaxine reach disproportionately higher peaks than desvenlafaxine concentrations in the initial 4 to 8 hours after maternal ingestion of venlafaxine and decline more precipitously thereafter. Consequently, desvenlafaxine makes a larger contribution to the breast milk concentrations in the second half of a 24-hour interval than estimates from 12-hour sampling would suggest. Taken together, these data indicate that desvenlafaxine is the largest contributor to infant exposure for women receiving venlafaxine therapy during lactation. Furthermore, the data suggest that administration of the newly approved desvenlafaxine during lactation would not appreciably lower infant exposure.

In summary, the current investigation confirms and extends previous investigations of venlafaxine exposure in nursing infants. Infant exposure during lactation while mothers are receiving venlafaxine therapy appears to be marginally higher than that for other antidepressants, largely as a consequence of the high level of infant exposure to desvenlafaxine. Nevertheless, the RID of 8.1% is within the notional 10% level of presumed safety, and there were no adverse events observed or reported in any of the infants in the current study.

Expanding the extant knowledge base on the use of venlafaxine in women choosing to breast-feed enhances the clinician's ability to inform women regarding the risks and benefits of breast-feeding. Similarly, by understanding the methodological limitations and differences across investigations, the clinician is equipped to interpret future investigations and apply such data to clinical scenarios.

Despite the acknowledged benefits of breast-feeding and general support for nursing by professional organizations, decisions regarding antidepressant exposure during lactation warrant careful deliberation. In women choosing to nurse, the patient and her clinician must consider (1) the extent of nursing infant exposure during ongoing central nervous system development, (2) the potential hazards of switching medications for women who are breast-feeding (exposing the neonate to multiple medications and risking a relapse of maternal illness), and (3) appropriate monitoring of nursing infants exposed to antidepressants.

Drug names: buspirone (BuSpar and others), desvenlafaxine (Pristiq), quetiapine (Seroquel), venlafaxine (Effexor and others).

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