The Pharmacokinetics of Sertraline Excretion Into Human Breast Milk: Determinants of Infant Serum Concentrations

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Background: The purpose of this study was to attain a new landmark in the area of selective serotonin reuptake inhibitor therapy during lactation by establishing a basis for interpreting infant serum concentrations and for minimizing infant exposure in the absence of treatment-emergent side effects.

Method: Breast milk and paired maternal and infant sera were collected following maternal treatment with sertraline monotherapy (25–200 mg/day) administered once daily. Sertraline and its major metabolite were measured in breast milk and serum samples using high-performance liquid chromatography with UV detection (limit of detection = 2 ng/mL).

Results: Twenty-six nursing women with DSM-IV major depressive disorder participated in the study; the mean (SD) daily sertraline dose was 123.9 (62.8) mg/day. Fifteen women submitted 182 breast milk samples for analysis of gradient (foremilk to hindmilk) and time course of medication excretion. The milk/plasma ratio was highly variable (range, 0.42–4.81). A significant gradient and time course of excretion for both sertraline ($p < .001$ for both) and desmethylsertraline ($p < .001$ for gradient and $p < .046$ for time course) were observed, with the highest concentrations observed in the hindmilk 8 to 9 hours after maternal ingestion. Mathematical modeling of sertraline and desmethylsertraline excretion revealed that discarding breast milk 9 hours after maternal dose decreased the infant daily dose of sertraline by a mean of 17.1% (1.8%). Twenty-two mother/infant sera pairs were obtained. Sertraline was detectable in 4 infants (18% of sample), and desmethylsertraline was found in 11 infants (50% of sample). The mean (SD) maximum calculated nursing infant dose of sertraline, 0.67 (0.61) mg/day, and desmethylsertraline, 1.44 (1.36) mg/day, represented 0.54% (0.49%) of the maternal daily dose. The maximum infant dose of desmethylsertraline ($p < .002$) significantly correlated with infant serum desmethylsertraline concentrations (ng/mL). In contrast, maternal daily dose, duration of medication exposure, and infant age and weight at sampling did not correlate with either detectability (< 2 ng/mL vs. ≥ 2 ng/mL) or absolute concentrations (ng/mL) in infant serum. No adverse events were reported or documented in any infant.

Conclusion: These results extend previous studies by demonstrating the utility of breast milk analysis in interpreting infant serum concentrations and minimizing infant exposure.

(J Clin Psychiatry 2003;64:73–80)

Received Feb. 18, 2002; accepted May 22, 2002. From the Department of Psychiatry and Behavioral Sciences (Drs. Stowe, Owens, Ritchie, and Nemeroff, Ms. Hostetter, and Mr. Sternberg), the Department of Gynecology and Obstretrics (Dr. Stowe), and the Department of Pathology (Dr. Ritchie), Emory University School of Medicine, Atlanta Ga.; and Harvard Medical School, Boston, Mass. (Dr. Cohen).

This work was supported by an unrestricted educational grant from Pfizer Pharmaceuticals and by the American Psychiatric Association SmithKline Beecham Young Faculty Award (Dr. Stowe).

Drs. Stowe and Nemeroff have served as consultants for, have received grant/research support and honoraria from, and have served on the speakers or advisory board for Pfizer. Dr. Cohen has received grant/research support from Forest, Janssen, Lilly, Wyeth-Ayerst, GlaxoSmithKline, and Berlex; has been a consultant for Lilly, Janssen, Solvay, Wyeth-Ayerst, and GlaxoSmithKline; and has been on the speakers bureau for Lilly, Janssen, Pfizer, GlaxoSmithKline, Wyeth-Ayerst, and Forest.

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The available data on antidepressant use, particularly selective serotonin reuptake inhibitors (SSRIs), in breastfeeding have rapidly accrued since the comprehensive review by Wisner and colleagues in 1996.[1] The new literature includes a diverse conglomeration of case reports, case series, and more extensive investigations that have seldom employed similar methodologies[2] and therefore have precluded derivation of scientifically based treatment guidelines. There remains both international and North American disparity regarding the most valid method for monitoring nursing infants and quantifying infant exposure.

Several recent publications have utilized the milk/plasma ratio (M/P) to determine the weight-adjusted infant daily dose[3–5] as a means of comparing individual medications. Previous investigations have demonstrated the limited utility of such measures based on the pattern of excretion of antidepressants into human breast milk.[6–9] As

a result, infant serum monitoring has emerged as the more direct but unsubstantiated method for ascertaining infant exposure. The importance of research-quality assays for infant serum monitoring has been noted in the earlier review[1] and confirmed by Birnbaum and colleagues,[10] who demonstrated that infant serum concentrations from a variety of nonstandardized commercial laboratories seldom found detectable antidepressant concentrations in nursing infant sera. However, reports utilizing research-quality assays with improved sensitivity for detection of fluoxetine,[11] paroxetine,[9,12] and sertraline[7,13–15] have typically demonstrated undetectable (< 2 ng/mL) or very low nursing infant serum concentrations as well. In addition to infant serum concentration measures, the effects of sertraline exposure in nursing infants on purported peripheral markers of serotonergic neurotransmission were investigated.[16] In that study, Epperson and colleagues measured infant platelet levels of serotonin before and after exposure to sertraline through breast milk. No significant change in nursing infants' platelet serotonin levels was found; however, there was considerable variability in the measures limiting definitive conclusions.[16] Despite the variety of approaches, no consensus on the most clinically relevant method of assessing nursing infant exposure to antidepressants has been attained. The limited number of reports demonstrating relatively high serum concentrations and purported adverse effects (fluoxetine, 3; sertraline, 1; citalopram, 1)[17] underscores the difficulty in interpreting the current literature.

More rigorous investigations have sought to calculate infant exposure by examining the pharmacokinetics of antidepressant excretion into breast milk and infant serum concentrations for fluoxetine,[6,18,19] paroxetine,[9] sertraline,[7] and venlafaxine.[8] These studies have largely confirmed the limited number of nursing infant serum samples with detectable medication concentrations. Moreover, they have provided the initial data necessary to develop strategies for minimizing nursing infant exposure to SSRIs. However, despite their seminal contributions, these studies have been unable to provide the clinician with definitive guidelines for the utility of breast milk analysis and the interpretation of infant serum measures. The clinical significance, if any, of detectable or comparably high infant serum concentrations remains unknown.

In the present study, we sought to expand our previous work in this area by further characterizing the excretion of sertraline into breast milk, calculating the maximum infant daily dose, and investigating the factors that influence the detectability and absolute concentrations in infant serum. Only novel data such as these are able to assist in the clinical interpretation of infant serum measures in the absence of treatment-emergent side effects.

Moreover, we sought to attain additional outcome data on infant sertraline exposure and additional pharmacokinetic data to aid in the development of strategies to minimize infant exposure.

METHOD

Subjects

Twenty-six postpartum women with a DSM-IV diagnosis of major depressive disorder (as established by clinical interview with a psychiatrist) who were treated with sertraline monotherapy constituted the subject sample. Each subject and her partner were informed of the available treatment options, including psychotherapy, electroconvulsive therapy, and other antidepressants, as well as the unknown risks associated with nursing during treatment with sertraline. All subjects participating in the current study requested infant serum monitoring as part of their clinical treatment plan and consented to have these values used as part of a research study. Written informed consent was also obtained for breast milk and maternal serum collection.

Sample Collection

All serum and breast milk samples were obtained after maternal serum sertraline concentrations had attained steady state (> 14 days on a fixed dose). Maternal blood, infant blood, and breast milk samples were collected as previously described in detail.[7,9] 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 gradient analysis (10-mL aliquots from foremilk to hindmilk). The samples were coded and stored at –80ºC (–112ºF) until assay. Laboratory personnel were blind to maternal daily dose and collection time of the samples.

Determination of Breast Milk and Serum Concentrations of Sertraline and Desmethylsertraline

Breast milk sample analysis consisted of both a liquid/liquid and solid phase extraction (100-mg EXTRASEP C18, Nalge Nunc, Int., Rochester, N.Y.) followed by high-performance liquid chromatography (HPLC) separation and UV detection. Determination of sertraline in serum utilized only the solid phase extraction procedure. The quantification was accomplished via an isocratic HPLC separation using 100 × 2 mm stainless steel Keystone Scientific MOS-2 Hypersil (C8) reverse phase column (Keystone Scientific, Bellefonte, Pa.), 3 μm, followed by UV detection at 215 nm. The analysis was performed with a model 1100 Hewlett Packard HPLC Chemstation equipped with a diode array detector (Hewlett Packard, Wilmington, Del.). The mobile phase consisted of 0.02 M potassium phosphate monobasic, 110 μL N,N-demethyloctylamine/L, 38% acetonitrile (pH 6.2). The flow rate of the mobile phase was set at 0.6 mL/minute.

Calibration curves were constructed from medication-free human breast milk by the addition of varying amounts of sertraline (0.0–500 ng). A 5-point standard curve and 2 quality control specimens were included in each assay. The limit of detection was 2.0 ng/mL (3 × signal to noise). Average correlation coefficients of variation were ≤ 5% intra-assay and ≤ 10% interassay at concentrations of 75 and 300 ng/mL.

Data Analysis

Breast milk concentration was divided by maternal serum concentration to provide the M/P ratio for each aliquot of breast milk obtained. The effects of maternal daily dose and maternal serum concentrations of sertraline on breast milk concentrations were assessed with linear regression using minimum and maximum breast milk concentrations observed for each participant. To determine the excretion gradient into breast milk, the concentration for each fraction was divided by that of the minimum observed concentration ($[BM_{min}]_g$) (typically the first 10-mL aliquot) and presented as a ratio from "fore" milk to "hind" milk. The time course was calculated in similar fashion using the minimum breast milk concentration ($[BM_{min}]_t$) (typically 22–24 hours after maternal dose).

Maximum daily infant dose ($InfDose_{max}$) of sertraline and desmethylsertraline was calculated by summation of the gradient area under the curve. These values were then summed at each time post dose (t, hours) that a given subject reported nursing. This total was multiplied by 2 to account for both breasts. This method of calculation assumes that the infant completely empties both breasts at each feeding, potentially providing an overestimation of infant dose and yielding the most conservative calculations. The potential relationship between the $InfDose_{max}$ and infant serum concentrations was assessed via linear regression. Potential determinants of infant serum detectability (< 2 ng/mL vs. ≥ 2 ng/mL) and absolute infant serum concentration (ng/mL) including maternal daily dose, maternal serum concentrations, gestational age at delivery, infant age and weight at sampling, duration of medication exposure, and maximum calculated infant daily dose were compared via the Student t test for detectability (< 2 ng/mL vs. ≥ 2 ng/mL) and linear regression for absolute infant sera concentration (ng/mL).

Infant Outcome

A formal infant assessment was not performed in the current study; however, all participants were asked upon direct interview the following questions: if the child had regular pediatric visits, if the pediatrician was informed of maternal sertraline use, and if the pediatrician had volunteered any comments concerning growth or infant development that warranted concern. Additionally, the parents who started medication after delivery (N = 14) were asked if they had noted any alteration in infant behavior, disposition, sleep, activity, or change in bowel movements after initiating sertraline treatment.

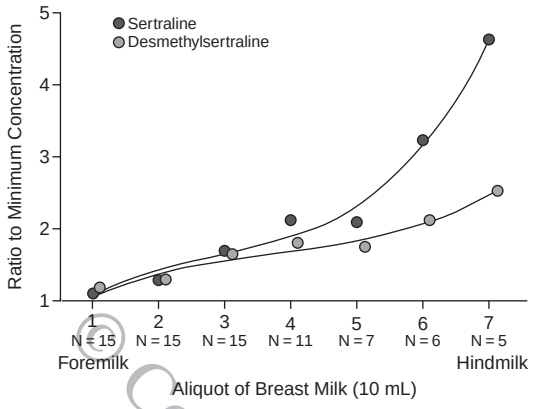
RESULTS

Twenty-six postpartum women treated with sertraline, mean (SD) dose = 123.9 (62.8) mg taken once daily, were included in the study. Twenty-three of these women received all of their treatment at our site; the remaining 3 participants contacted the program for breast milk and serum analysis. A total of 182 breast milk samples and 22 maternal/infant serum pairs were obtained. Twelve milk samples were excluded from final data analysis secondary to improper labeling (5), collection on different days (4), failure to maintain frozen state prior to arrival at Emory (2), and inadequate volume for protocol (1). This resulted in a total of 170 breast milk samples, 86 for gradient analysis and 84 for time course analysis. Fifteen participants submitted breast milk samples for both gradient and time course analysis, and 11 of these participants had complete sets of data (breast milk collection for gradient and time course, and maternal and infant sera) utilized in the assessment of the predictors of infant serum concentration.

Detectable concentrations of sertraline, mean (SD) = 129.2 (159.5) ng/mL (range, 11–938 ng/mL), and desmethylsertraline, mean = 257.7 (262.6) ng/mL (range, 20–1498 ng/mL), were present in all breast milk samples. The M/P ratio was highly variable (range, 0.42–4.81). Fifteen subjects submitted breast milk samples (total = 86 samples) for gradient excretion analysis of sertraline and desmethylsertraline concentrations. A significant volume/aliquot-dependent rate of excretion, with increased concentrations in later aliquots of breast milk (hindmilk), was observed for both parent compound and metabolite. The data were best fit via third-order polynomial regression for sertraline ($R = 0.52$, $F = 9.937$, $df = 3,85$; $p < .001$) and desmethylsertraline ($R = 0.64$, $F = 18.512$, $df = 3,85$; $p < .001$); data shown in Figure 1.

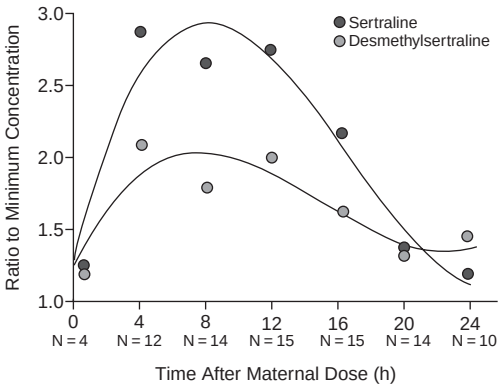
The time course of excretion into breast milk for sertraline and desmethylsertraline, defined as the breast milk concentration at various timepoints following maternal dosage, was determined for 15 women who collected > 3 samples in a 24-hour period (total = 84 samples). To control for the gradient effect, the sample obtained at each timepoint was the initial 10 mL (foremilk) of breast milk. Similar to our previous investigation,[7] a significant time course for both the parent compound and major metabolite was observed. These data were best described by a third-order polynomial regression for sertraline ($R = 0.49$, $F = 8.313$, $df = 3,83$; $p < .001$) and desmethylsertraline ($R = 0.31$, $F = 2.782$, $df = 3,83$; $p = .046$); data shown in Figure 2. Mathematical modeling of sertraline and desmethylsertraline excretion revealed that discarding

Figure 1. Gradient for Sertraline and Desmethylsertraline Excretion Into Human Breast Milk[a]



[a]Mean ratio of sertraline and desmethylsertraline concentrations to the minimum breast milk concentration in each set of samples plotted by the aliquot of breast milk obtained from 15 women. Fifteen women submitted breast milk samples (> 3 samples each, total number of samples = 86) for determination of gradient effects from foremilk to hindmilk. The data for 74 samples up to 70 mL are shown in the figure (data not shown for 12 samples beyond 70 mL from an individual participant). The breast milk concentrations of both sertraline and desmethylsertraline increased from the initial portion of breast milk to the later portions of breast milk. The data shown represent breast milk samples collected from a single breast 8 to 12 hours after maternal oral daily dose of sertraline. These sertraline data were significantly defined by a third-order polynomial; sertraline, correlation coefficient (R) = 0.52, F = 9.937, df = 3,85; p < .001; and desmethylsertraline, R = 0.64, F = 18.512, df = 3,85; p < .001.

Figure 2. Time Course of Sertraline and Desmethylsertraline Excretion Into Human Breast Milk[a]



[a]Mean ratio of sertraline and desmethylsertraline concentrations to the minimum breast milk concentration in each set of samples plotted by the time after maternal ingestion of sertraline for 15 women. Fifteen women submitted breast milk samples (> 3 samples each within a 24-hour period, total number of samples = 84) for determination of the time course of excretion into breast milk. These data were best described by a third-order polynomial; sertraline, correlation coefficient (R) = 0.49, F = 8.313, df = 3,83; p < .001; and desmethylsertraline, R = 0.31, F = 2.782, df = 3,83; p = .046.

breast milk 8 to 9 hours after maternal dose decreased the infant daily dose of sertraline by a mean of 17.1% (1.8%).

In contrast to the results of our recent investigation of paroxetine,[9] there was a significant relationship between both minimum (R = 0.83, F = 22.87, df = 1,11; p < .001) and maximum (R = 0.93, F = 64.67, df = 1,11; p < .001) breast milk concentrations with maternal serum sertraline concentrations but not maternal daily dose (data not shown).

Serum samples were obtained from 22 nursing mothers and their infants; the remaining 4 women who participated in the study declined infant serum collection. The majority of sample pairs were obtained on the same day (N = 20), and the remaining sample pairs were collected within 5 days of each other. Maternal serum was obtained 2 to 26 hours after daily dose, mean (SD) = 7.9 (6.8) hours, and infant serum samples were obtained 0.5 to 5 hours after nursing, mean = 2.2 (1.7) hours. All infants but 1 had term deliveries, gestational weeks based on last menstrual period; mean = 38.8 (2.2) weeks. Infant age and weight were variable across the group: mean = 16.6 (9.4) weeks and mean = 6.1 (1.6) kg, respectively. The majority of infants (91%, N = 20) were fully breastfed and received no supplemental nutrition. Eleven infants had detectable concentrations of desmethylsertraline, mean = 21.9 (39.6) ng/mL, and 4 of these infants also had detectable concentrations of sertraline. These data are presented in Table 1.

One infant (pair V) had serum concentrations of sertraline (87 ng/mL) and desmethylsertraline (145 ng/mL) that were higher than maternal serum concentrations. It is noteworthy that infant V was being actively treated for severe asthma at the time of sampling, and the infant was concurrently receiving albuterol treatments, inhaled steroids, and hydroxyzine as needed for agitation from the respiratory treatments. The mother declined repeat infant serum analysis secondary to infant distress during the initial blood draw. This infant received the fifth highest $InfDose_{max}$ of sertraline (0.389 mg/day) and desmethylsertraline (1.194 mg/day) and was considered an extreme outlier on the basis of infant sera level relative to this projected dose. This infant was excluded from the analysis of $InfDose_{max}$ effects on infant serum concentrations given the potentially confounding asthma treatments.

The mean (SD) maximum calculated nursing infant dose of sertraline, 0.67 (0.61) mg/day, and desmethylsertraline, 1.44 (1.36) mg/day, represented 0.54% (0.49%) of the maternal daily dose. The best predictor of infant serum desmethylsertraline concentrations was the calculated maximum infant daily dose ($InfDose_{max}$) of desmethylsertraline (R = 0.86, F = 22.0, df = 1,9; p < .002). The calculated maximum infant daily dose ($InfDose_{max}$) of sertraline did not predict infant serum desmethylsertraline concentration. The insufficient number of samples with detectable sertraline concentrations precluded analysis of predictors of infant serum sertraline concentrations. Infor-

Table 1. Maternal and Infant Treatment Characteristics for Infants With and Without Detectable Serum Concentrations of Sertraline and Desmethylsertraline

	Infant Serum (ng/mL)		Maternal Serum (ng/mL)		Maternal Medication		Infant[a]				Minimum Concentration in Breast Milk (ng/mL)		Maximum Calculated Infant Dose (mg/d)[c]	
Maternal-Infant Pair	Sertraline	Desmethyl-sertraline	Sertraline	Desmethyl-sertraline	Dose (mg/d)[a]	Start of Medication	Age at Sample (wk)	Weight (kg)	Nursing Freq/d	Medication Exposure (wk)[b]	Sertraline	Desmethyl-sertraline	Sertraline	Desmethyl-sertraline
Infants with undetectable serum concentrations														
A	< 2.0	< 2.0	2	30	25	Pregnancy	5	4.7	7	16	NA	NA	NA	NA
B	< 2.0	< 2.0	42	90	50	Postpartum	12	6.4	8	3	20.2	32.4	0.17	0.21
C	< 2.0	< 2.0	21	61	50	Pregnancy	5	4.1	10	11	NA	NA	NA	NA
D	< 2.0	< 2.0	12	129	75	Postpartum	17	5.5	6	13	16	106	NA	NA
E	< 2.0	< 2.0	30	56	100	Postpartum	16	NA	5[d]	16	NA	NA	NA	NA
F	< 2.0	< 2.0	26	95	100	NA	NA	NA	NA	NA	NA	NA	NA	NA
G	< 2.0	< 2.0	40	97	100	Pregnancy	7	3.7	8	47	21	57	0.18	0.37
H	< 2.0	< 2.0	36	150	150	Postpartum	28	7.7	8	22	NA	NA	NA	NA
I	< 2.0	< 2.0	44	172	150	Pregnancy	22	7.8	6	43	NA	NA	NA	NA
J	< 2.0	< 2.0	74	531	200	Pregnancy	24	7.2	5[d]	63	132	493	0.27	0.77
K	< 2.0	< 2.0	36	105	200	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mean			33.00	137.82	109.09	55.5% in	15.11	5.89	7	26.00	47.30	172.10	0.21	0.45
SD			17.97	130.41	56.68	Pregnancy	8.01	1.52		18.97	48.94	187.16	0.05	0.24
Infants with detectable serum concentrations														
L	< 2.0	2.5	72	588	250	Pregnancy	11	5.5	7	49	NA	NA	NA	NA
M	< 2.0	4	13	122	75	Pregnancy	26	7.9	9	37	8.4	30.4	0.37	0.74
N	< 2.0	5	63	466	200	Pregnancy	24	8.9	6	30	NA	NA	NA	NA
O	< 2.0	6	58	356	50	Pregnancy	5	4	9	46	29	95.4	1.03	2
P	< 2.0	7	21	55	50	Pregnancy	7	5.7	7–8	47	20	59	0.89	1.57
Q	< 2.0	8	77	159	100	Pregnancy	24	5.7	6[d]	34	57	50.3	0.37	1.82
R	< 2.0	28	93	219	150	Postpartum	4	3.5	6	42	56	215	2.25	5.1
S	2	18	206	951	200	Pregnancy	22	6.9	8	61	290	514	0.85	1.36
T	3	11	132	821	200	Postpartum	36	8.3	6	20	NA	NA	NA	NA
U	7	6	36	114	100	Postpartum	12	5.3	6	6	16.8	40.5	0.26	0.44
V	87	145	24	126	150	Postpartum	11	7.3	6	6	29	125	0.39	1.19
Mean		21.86	72.27[e]	361.55[f]	138.64	63.6% in	16.55	6.27	6.9	34.40	63.28	141.20	0.80	1.78
SD		39.58	53.92	293.91	65.16	Pregnancy	9.88	1.66		16.84	87.24	151.75	0.61	1.35

[a]At time of infant serum sampling.
[b]Total fetal and neonatal exposure = medication in pregnancy (wk) + duration of nursing infant exposure (wk) at time of infant serum sampling.
[c]Maximum calculated infant dose (µg/day) =

$$\text{InfDose}_{\max}\ (\text{sertraline}) = 2\left[\sum_{t=x_1}^{t=x_n}\left(\left[\int_1^{\infty} 1.528 - (0.598a) + (0.236a^2) - (0.0139a^3)(10\ \text{mL/aliquot})\right][\text{BM}_{\min}]_t\right)\right]$$

$$\text{InfDose}_{\max}\ (\text{desmethylsertraline}) = 2\left[\sum_{t=x_1}^{t=x_n}\left(\left[\int_1^{\infty} 0.809 + (6.298a) - (0.0167a^2) + (0.000466a^3)(10\ \text{mL/aliquot})\right][\text{BM}_{\min}]_t\right)\right]$$

a = aliquot of breast milk from foremilk to hindmilk (1–∞)(10 mL/aliquot); the equation between the inner bracket [ ] represents area under the curve for the gradient; $[\text{BM}_{\min}]_t$ = the minimum breast milk concentration (typically the first 10-mL aliquot) at a given time (t) in hours after maternal dose in µg/mL; x_1 = time (h) of initial breastfeed based on a 24-hour clock; x_n = the time of all subsequent breastfeeds in the same 24-hour period. This total is multiplied by 2 to account for both breasts.
[d]Supplemental feedings > 2 per day.
[e]p = .033, Student t test for maternal sertraline concentration in infants with detectable versus undetectable serum concentrations.
[f]p = .032, Student t test for maternal desmethylsertraline concentration in infants with detectable versus undetectable serum concentrations.

mal assessment of infant outcome indicated that there were no acute observable adverse effects reported in any of the 26 infants.

DISCUSSION

The current study confirms and extends previous observations of the highly variable concentrations of both sertraline and desmethylsertraline in human breast milk. These results are remarkably concordant with our previous sertraline investigation,[7] demonstrating a similar time course for sertraline and desmethylsertraline excretion with peak concentrations observed 8 to 9 hours after maternal daily dose. The relatively large number of breast milk samples obtained in the current study allowed significant characterization of the gradient of excretion of sertraline and desmethylsertraline, with the highest concentrations of both seen in the more lipophilic hindmilk. These data provide a strategy for significantly reducing nursing infant exposure to sertraline (calculated decrease of 17.1%) by discarding the breast milk at 8 to 9 hours after maternal medication ingestion. All nursing women should be informed that the "pump and dump" option would decrease infant daily dose.

These data, like those obtained with fluoxetine,[6,18] paroxetine,[9] and venlafaxine,[8] underscore the limitations of the milk-to-plasma ratio, without control for gradient and time effects, as an accurate measure for determining infant exposure. The clinical utility of breast milk analysis is not limited to mechanisms for minimizing infant exposure, but includes application in the interpretation of infant serum measures. The significant correlation between the maximum calculated infant daily dose determined from breast milk analysis and infant serum concentrations of desmethylsertraline suggests that additional analyses such as these may serve to establish guidelines for breast milk concentrations that may reliably predict detectable infant serum concentrations. A total of 18.2% of infant serum samples (4 of 22) had detectable concentrations of sertraline, and 50% (11 of 22) had detectable concentrations of desmethylsertraline. The proportion of detectable infant sera was similar to that found in our previous investigation,[7] with detectable infant serum concentrations of sertraline and desmethylsertraline in 27.2% and 54.5% of infants, respectively. However, the maximum calculated infant daily dose was higher than in our previous report.[7] This result is most likely secondary to the inclusion of gradient effects, which was not possible in the previous investigation, and the increased methodological rigor in having women collect breast milk for both time and gradient analysis.

The infant with high serum concentrations (pair V) is of interest. While no treatment-emergent side effects were apparent, this particular case raises a topic that is not discussed in the current literature: the potential impact of other medications on the nursing infant metabolism of antidepressants and whether or not such compounds impede accurate analysis. The previous case reports that have identified high concentrations of SSRIs in nursing infant sera[17] proposed explanations of either erroneous laboratory values or possible accumulation in infant serum. In the absence of repeated infant serum measure in this study, laboratory error is a possibility. However, a more conservative approach suggests that such a higher steady state in infant serum could be attributable to other infant medications (e.g., pair V), infant metabolic maturity, or differences in pharmacogenetics.[20] In support of the latter, mothers of infants with detectable serum concentrations had significantly higher serum concentrations of both sertraline and desmethylsertraline, despite the absence of a significant difference in maternal daily dose. This finding may suggest that these women metabolize sertraline at a variable rate. However, the correlation of minimum and maximum breast milk concentrations of sertraline with maternal serum concentration indicates that this may be an infant dose–related phenomenon rather than a reflection of infant metabolic capacity. A recent study by Öhman and colleagues[5] explored the former possibility by assessing maternal metabolic enzymes, the underlying assumption being that the neonate possesses the same enzymes. These purported outliers may ultimately provide the greatest insight in the understanding of psychotropic medication disposition in the nursing infant. For this pair to be considered a true "outlier," the factors that directly influence infant serum concentrations such as infant daily dose and/or maternal serum concentrations need to be confirmed.

The current literature, including recent presentations at national meetings, have reported on greater than 200 nursing infant serum measures of the SSRIs citalopram,[21,22] fluoxetine,[10,11,18,19] fluvoxamine,[3,15,23] paroxetine,[9,10,12,15] and sertraline.[7,10,13–16,24] Despite the burgeoning data, purported adverse effects are limited.[17] Further, the recent study by Epperson and colleagues[16] demonstrated no significant effects of sertraline exposure via breast milk on platelet serotonin in infants. While reassuring, this is not surprising considering the maximum possible infant dose encountered in the present study. The absence of acute treatment-emergent adverse effects limits any definitive clinical direction in choosing appropriate pharmacotherapy for lactating women. While the majority of studies have failed to detect SSRIs in nursing infant sera, the question of how to interpret such data remains obscure. Basing clinical decisions on absolute infant serum concentrations (ng/mL) in the absence of controlled data to interpret such findings is ill-conceived. Such simple comparisons (ng/mL) fail to account for the large variation in affinities for monoamine transporters and receptors between the individual SSRIs.[25–27] Furthermore, no consensus for utilization/transformation of undetect-

able nursing infant sera concentrations in data analysis has been reached. Our group has consistently used a conservative conversion of these values to the limit of detection (e.g., < 2 ng/mL = 2 ng/mL). The absence of a consensus and the myriad of methodological differences among studies make combining data difficult. Similarly, the extension of in vitro binding data to neonatal central nervous system tissue is unknown. Medication selection prior to further data on neonatal metabolic capacity (e.g., infant sera, infant dose, infant excretion) and potential functional exposure accounting for binding affinities is premature. As such, the best medication choice is the one with proven efficacy for a given individual. Additional factors to consider include data in breastfeeding, prior exposure during pregnancy, and reasonable acceptability to the infant's clinician.

The focus of the current study was to further our interpretation of infant serum concentrations. The sample size and inclusion of breast milk sampling allowed for an initial investigation of the potential factors that predict both infant serum detectability (< 2 ng/mL vs. ≥ 2 ng/mL) and absolute infant serum concentration (ng/mL). While it is not surprising that factors directly influencing infant daily dose account for detection in infant serum, this study is the first to confirm such a relationship. The failure to demonstrate a relationship between maternal daily dose and infant serum concentrations underscores the potential utility of breast milk analysis and maternal serum concentrations in the interpretation of infant serum measures. These results provide a preliminary framework for establishing breast milk and maternal serum concentrations that predict infant serum detectability. Knowing both the infant daily dose and infant serum concentration provides the initial foray into assessing infants' metabolic capacity for these compounds.

Despite the ability to more accurately quantify nursing infant exposure to medications, the limited lactation-specific laboratory data preclude any conclusions about potential sequestration in more lipophilic infant tissues such as the central nervous system. It is reassuring that no acute adverse events were reported in the current study despite the variability in infant daily dose and infant serum concentrations. Pending definitive neurobehavioral investigations, the clinician should consider any alternative to minimize infant exposure to medications such as discarding breast milk at peak concentration times.

CONCLUSION

The current study represents an incremental advance in the relative safety data of SSRIs during lactation by providing novel information on the predictors of infant serum concentrations and a method for significantly reducing nursing infant exposure. As further data are obtained, it is feasible that both breast milk and maternal serum concentration guidelines (e.g., minimum concentrations for detectability in infant serum) could be established. Until such guidelines are confirmed, routine infant serum monitoring in the absence of suspected side effects remains difficult to interpret. Breast milk and maternal serum concentration limits, if determined and confirmed, will enable the clinician to ascertain if the infant serum concentrations represent potential outliers warranting re-evaluation of the decision to continue breastfeeding while taking medication and may serve to eventually spare the mother and infant the stress of infant serum collection.

Drug names: albuterol (Proventil, Ventolin, and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), hydroxyzine (Vistaril, Atarax, and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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