Sertraline and Desmethylsertraline in Human Breast Milk and Nursing Infants

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Objective: *The purpose of this study was to determine the concentrations of sertraline and desmethylsertraline in both human breast milk and infant serum.* *Method:* *Breast milk samples from 12 women were collected at specific time intervals after oral doses of sertraline (25–200 mg once daily). For 11 mother-infant pairs, maternal serum levels 24 hours after a dose and their infants' serum levels 2–4 hours after nursing were ascertained by high-performance liquid chromatography.* *Results:* *Sertraline and desmethylsertraline were present in all breast milk samples, with a gradient from "fore" milk to "hind" milk. The highest concentrations of sertraline were observed in hind milk 7–10 hours after maternal dose. Increasing the maternal dose of sertraline resulted in increased breast milk concentrations of both sertraline and desmethylsertraline. Detectable concentrations of sertraline were found in three nursing infants and desmethylsertraline in six. No adverse effects of exposure were observed in any infant.* *Conclusions:* *Sertraline and desmethylsertraline were present in the breast milk of nursing women treated with sertraline. Concentrations were affected by aliquot of milk sampled, time after maternal dose, and maternal daily dose. The infants' serum concentrations detected were below the detection limit of most commercial laboratories. The presence of desmethylsertraline in six infants' samples underscores the importance of metabolite monitoring in determining infant exposure. Estimates of daily infant exposure can be determined after analysis of sertraline and desmethylsertraline concentrations from one full breast at maternal serum steady state. Future studies of breast milk and infant serum samples should address these issues.*

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Pregnancy and childbirth represent a period of unique neuroendocrine and psychosocial adjustment during which up to 10% of women meet criteria for major depression. Comprehensive reviews of the management of major depression during pregnancy and lactation focus predominantly on pregnancy (1–5). However, the increasing number of nursing mothers (6) and the numerous professional groups that support breast milk as the ideal form of infant nutrition underscore the need to conduct definitive studies of the transmission of antidepressants to infants during lactation. In a review of the available breast-feeding data, Wisner and colleagues (7) demonstrated the limited quantity of meaningful data.

Medications enter breast milk primarily by passive diffusion of the free fraction (8), while specific physiochemical properties of a drug appear to be the best predictor of drug concentrations present in breast milk (9). These properties include: 1) degree of ionization, which is a function of the pKa, 2) molecular weight, 3) blood protein binding, and 4) lipid solubility. The pH gradient between maternal serum and breast milk is a major determinant of the quantity of drug excreted into the milk.

Neonatal physiology exhibits unique characteristics that may result in increased circulating drug concentrations after oral dosing relative to that in older individuals. Hepatic maturation in the infant appears to occur at a highly variable rate (10) and is even more delayed in premature infants. Both glucuronidation and oxidative systems are immature at birth (as low as 20% of adult levels); the latter system typically matures by 3

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months of age (11). In addition, glomerular filtration rate and tubular secretion are relatively low in neonates: 30%–40% and 20%–30% lower than adult levels, respectively (12).

The excretion of psychotropic medications in breast milk has been reviewed in the past several years (13, 14). To date, all antidepressants studied have been found in breast milk; the milk-to-serum ratio is typically ≥1.0 (13). These studies are confounded by differences in breast milk collection techniques, limited sample sizes, and different drug assay methods. The majority of such studies have been conducted with tricyclic antidepressants (7). Wisner and Perel (15, 16) reported on 12 nursing women treated with nortriptyline. Although no infant serum samples had detectable nortriptyline levels, detectable levels of 10-hydroxy-nortriptyline were found in two infants. The same group did not find detectable serum concentrations of clomipramine and its major metabolites in four nursing infants (17). Case reports are available on fluoxetine (18–20), fluvoxamine (21), and sertraline (22). Recently, a more detailed study (23) demonstrated an effect of the amount of time after maternal dose on the concentration of fluoxetine and norfluoxetine in breast milk. Such time course data for the excretion of antidepressants into breast milk could provide a means of minimizing infant exposure, i.e., discarding breast milk during peak concentrations. Despite the limited database, most reviews support the use of secondary amine tricyclic antidepressants (nortriptyline and desipramine) as first-line agents to treat major depression in nursing women (1, 2).

The U.S. Food and Drug Administration has not approved any antidepressant for use during lactation, and the American Academy of Pediatrics (24) listed fluoxetine and fluvoxamine as having "effects unknown but [that] may be of concern," with no comment regarding the use of sertraline or paroxetine. Pons et al. (14) discouraged the use of fluoxetine in lactating women because of its relatively long half-life of elimination. The purpose of the current study was to determine concentrations of sertraline and desmethylsertraline in the breast milk of women who chose to continue nursing during treatment and in the serum of their infants.

METHOD

Twelve nursing women who came to the Emory University Pregnancy and Postpartum Mood Disorders Program with depressive symptoms or a history of depression were included in the study. Three women were treated with sertraline during pregnancy, two women were treated postpartum with sertraline for prevention of recurrent postpartum depression, and seven were treated with sertraline for postpartum-onset major depression. All subjects were interviewed by a psychiatrist (Z.N.S.). Each subject and her spouse were informed of the available treatment options, including psychotherapy, ECT, and other antidepressants, and the unknown hazards of continuing to nurse during treatment with sertraline. All subjects participating in the study requested infant serum monitoring as part of their clinical treatment plan. Written informed consent was obtained, and collection protocols for the maternal serum, infant serum, and breast milk samples were reviewed with each subject. All subjects were either continued on their present dose regimen of sertraline or started on sertraline, 25 mg/day p.o., once daily in the morning. The sertraline dosage was adjusted at 1- to 2-week intervals until depressive symptoms improved or a maximum daily dose of 200 mg/day was achieved.

Maternal and infant blood samples were obtained, after maternal serum concentrations reached a steady state (more than 14 days on a fixed dose) in Vacutainer tubes without additives. Blood was centrifuged at 950 *g* for 10 minutes, and the serum was removed and transferred in 1-ml aliquots to sterile polypropylene tubes. The tubes were coded and stored at –80°C until assay.

All breast milk samples were collected from the same breast with the use of electric or manual breast pumps after the woman had been taking a fixed dose of sertraline for 14–21 days. Samples were collected by two different procedures. 1) Breast milk samples (the initial 20 ml) were collected from a single breast at 4- to 6-hour intervals, over a 24-hour period, to determine the impact of time after oral dose on breast milk concentration. Samples were stored in sterile polypropylene tubes. This procedure was repeated at each dose of sertraline for each subject. 2) Milk samples from a single breast were collected directly into the sterile tubes, in 10-ml aliquots from "fore" milk (the first 10–20 ml) to "hind" milk, 8–12 hours after an oral dose of sertraline to determine whether a concentration gradient for sertraline excretion exists in breast milk. The impact of maternal dose on breast milk concentrations was examined in six women who submitted breast milk samples while taking two different doses of sertraline. The women labeled and stored these samples in their home freezers. Milk samples were coded and stored at –80°C until assay.

Solvent was added to silanized glass screw-top tubes containing 200 ng of an internal standard (CP 53-630-1), saturated with sodium chloride, and the pH was adjusted by the addition of 150 µl of 2 M sodium hydroxide. Following the addition of 3 ml of hexane/butanol (98%/2%), the tubes were capped and the solvents were mixed by rotation for 10 minutes. After centrifugation (950 *g*), the aqueous layer was frozen in a dry ice/acetone bath, and the organic layer was transferred to another tube containing 1 ml of 0.025 N sulfuric acid. Following 10 minutes of rotation and subsequent centrifugation, the organic layer was aspirated, and 150 µl of 2 M sodium hydroxide and 3 ml of hexane/butanol (98%/2%) were added to the aqueous phase. Following mixing and centrifugation of the sample, the organic layer was transferred to a silanized conical-bottom tube and evaporated to dryness under a stream of nitrogen. The samples were resolvated in 50 µl of mobile phase just before injection onto the high-performance liquid chromatograph.

Isocratic high-performance liquid chromatography separations were performed with the use of a 150 × 4.6-mm stainless steel column packed with cyano-bonded microparticulate (5-µm) silica (Econex Sphere CN, Phenomenex, Torrance, Calif.). A constaMetric 4100 solvent delivery pump (LDC Analytical, Riviera Beach, Fla.) was used to deliver a mobile phase consisting of 12% 0.012 M sodium phosphate (pH=6.2), 38% acetonitrile, and 50% methanol at an isocratic flow rate of 1.5 ml/min. Detection was accomplished with a spectroMonitor 5000 photodiode array detector (LDC Analytical) at a wavelength of 215 nm. Individuals performing the drug concentration assays were blind to the maternal drug dose and milk sample (aliquot, time) conditions.

Calibration curves were constructed in 1-ml aliquots of either drug-free breast milk or serum by the addition of varying amounts of sertraline (0.5–400 ng) and desmethylsertraline (0.1–400 ng) and a constant amount (200 ng) of the internal standard. Standards were solvent-extracted and chromatographed as described for samples. The detector response (peak area) for sertraline and desmethylsertraline, relative to that of the internal standard, was calculated for each sample and standard. The concentrations of sertraline and desmethylsertraline in the samples were then calculated from their peak area ratios with use of the slope and intercept of the appropriate calibration curve. The assay had a lower limit of sensitivity of 1 ng/ml, defined by a signal-to-noise ratio greater than 7 for both sertraline and desmethylsertraline.

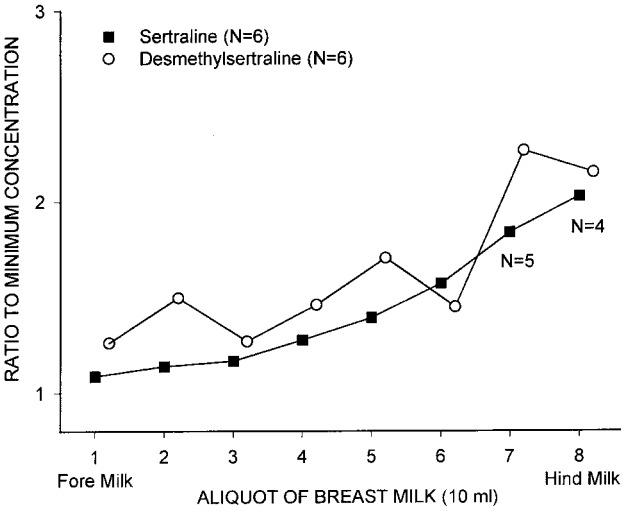
The ratios of sertraline and desmethylsertraline concentrations in breast milk were compared to ratios in maternal serum. To determine

the gradient in breast milk, the drug concentrations for each fraction were divided by that of the minimum observed concentration ($[BM_g]^{min}$) (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 by using the minimum breast milk concentration ($[BM_t]^{min}$) (typically, 22–24 hours after maternal dose). To assess the total daily infant dose, polynomial regression followed by integration to determine the area under the curve for breast milk gradients, time course, and correlation with maternal steady-state concentration were analyzed with use of the Mathematica 2.2 program (Wofram Research, Inc., Champaign, Ill.).

The impact of maternal daily sertraline dose on breast milk concentrations was determined by calculating the slope of the lines for the six women who submitted samples while taking two different doses of sertraline. The slopes of these lines represent the increase in breast milk concentration (in nanograms per milliliter) as a function of the increase in daily sertraline dose (in milligrams).

Infant daily dose of sertraline and desmethylsertraline was calculated as follows. 1) Sertraline and desmethylsertraline concentrations determined by high-performance liquid chromatography for the gradient of drug in fore milk to hind milk for each individual were summed to yield total drug per breast. 2) On the basis of the equation representing the amount of drug in breast milk at various times after dose relative to that actually observed, we calculated total drug per breast at each time point at which the mothers nursed in the 24-hour period. 3) Total drug per breast was summed for each individual feeding and multiplied by 2 (two breasts at each feeding) to yield total infant dose per day.

FIGURE 1. Mean Ratios of Sertraline and Desmethylsertraline Concentrations to the Minimum Breast Milk Concentration in Each Set of Samples Plotted by Aliquot of Breast Milk Obtained From Six Women[a]



[a]The lines connect the mean values, as a significant fit to a polynomial equation (limited to third order or less) was not possible. The data shown represent breast milk samples from a single breast that were collected 8–12 hours after the oral daily dose of sertraline.

RESULTS

A total of 148 breast milk samples and 17 maternal serum samples were obtained from the 12 participants; one subject declined collection of maternal serum. Analyzable breast milk samples were collected for gradient analysis from six of the 12 participants (N=45), for time course analysis from 12 (N=54), and for analysis of effects of increased maternal dose from six (N=12), accounting for a total of 111 samples. The primary reasons for exclusion of breast milk samples were failure to collect more than three samples in the same 24-hour period (N=12), failure to document which fraction of breast milk was collected (N=18), and failure to keep samples continuously frozen (N=7). Serum from 11 mother-infant pairs was obtained; one mother declined to have a second attempt at infant serum sampling.

Detectable concentrations of both sertraline (17–173 ng/ml) and desmethylsertraline (22–294 ng/ml) were present in all breast milk samples. The mean ratio of breast milk concentration to that of maternal serum was 2.3 (SD=1.3) for sertraline and 1.4 (SD=0.8) for desmethylsertraline.

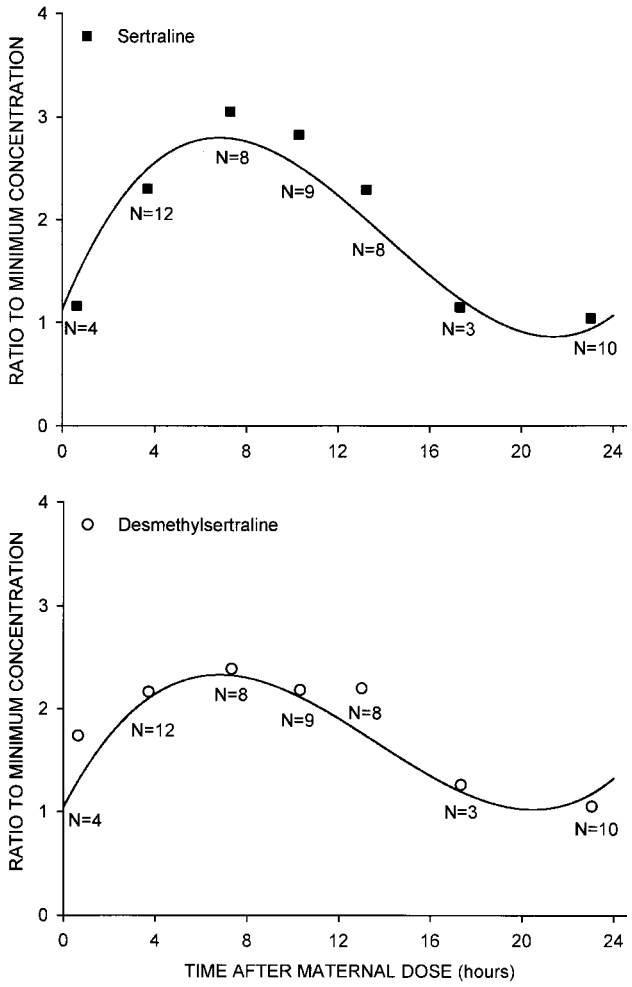
The breast milk concentrations of sertraline and desmethylsertraline were the lowest in the first 10–20 ml of breast milk, and the highest concentrations were observed in the more lipophilic hind milk—an approximate doubling relative to concentrations in the fore milk (figure 1).

In the analysis of the raw data on breast milk for each of the six subjects used for figure 1, both sertraline and desmethylsertraline showed volume/aliquot-dependent rates of excretion, with an underlying trend of increased sertraline and desmethylsertraline concentrations in later aliquots of breast milk. The multiple rates of excretion demonstrated in the gradient data are not adequately fitted by a polynomial regression, thereby making smooth integration (area under the curve) impossible. Treatment of these multiple-rate constants is best defined by plotting aggregate rates as a single power function (ml^{α}). The α values for each subject (data not shown) describe how the rate of excretion of sertraline and desmethylsertraline changes with volume/aliquot of expressed milk.

The time course for the excretion of sertraline and desmethylsertraline in breast milk—defined as the breast milk concentration at various time points after maternal dosage—was determined for 12 women, who collected more than three samples in a 24-hour period (N=54). Each sample obtained was the initial 10–20 ml of breast milk at each time point to control for the gradient effect. The concentration of sertraline in breast milk was maximal approximately 7–8 hours after dose, while the maximum desmethylsertraline concentration was observed over a longer period of 5–11 hours after dose. The relative mean maximum concentrations of sertraline and desmethylsertraline demonstrated a >300% and a >250% rise, respectively, compared to trough concentrations. Minimum concentrations were observed 22–24 hours after maternal oral dose and began to rise quickly after the next dose (figure 2).

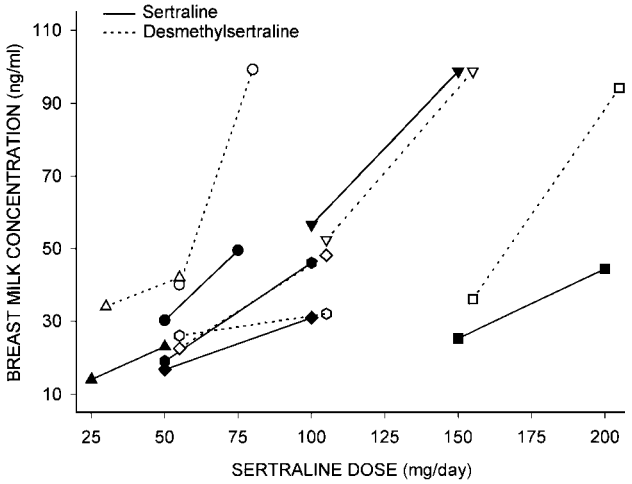
The time course of excretion of sertraline and of desmethylsertraline was significantly defined by a third-order polynomial regression fitted to the raw data: sertraline concentration relative to $[BM_t]^{min}$ at time $x=1.07 + 0.503x - 0.0428x^2 + 0.001x^3$ ($F=7.10$, df=3, 50, $p=0.01$); desmethylsertraline concentration ratio

FIGURE 2. Mean Ratios of Sertraline and Desmethylsertraline Concentrations to the Minimum Breast Milk Concentration for Each Individual for Each Set of Samples Plotted by Time After Maternal Oral Dose[a]



[a]All 12 subjects submitted at least three milk samples obtained in a single 24-hour period. The lines in both parts of the figure represent third-order polynomial regression fitted to the raw data (data not shown).

FIGURE 3. Effects of Maternal Sertraline Dose on Breast Milk Concentrations of Sertraline (solid symbols) and Desmethylsertraline (open symbols) Obtained From Six Women[a]



[a]Each individual symbol shape represents one subject's values for both sertraline and desmethylsertraline. The samples of breast milk were collected 8–12 hours after maternal oral dose of sertraline and represent the concentrations measured in the initial 10–20 ml.

relative to $[BM_t]^{min}$ at time $x=1.92 + 0.062x - 0.00752x^2 + 0.00015x^3$ ($F=4.28$, df=3, 50, $p=0.04$).

Six women submitted fore breast milk samples (10–20 ml) collected 8–12 hours after oral dose both before and after an increase in their daily dose of sertraline. In all cases, the breast milk concentrations of both sertraline and desmethylsertraline were increased compared to concentrations in samples obtained at lower total daily doses (figure 3).

Typically, an increase in the maternal daily dose of sertraline produced a more pronounced increase in the breast milk concentration of desmethylsertraline (Δ= 0.90 ng/ml per mg, SD=0.79) than of sertraline (Δ=0.53 ng/ml per mg, SD=0.23). In spite of the data shown in figure 1 and figure 3, with the small group size (N=6), we found only moderate positive correlations between mean breast milk concentrations of sertraline, desmethylsertraline, and sertraline plus desmethylsertraline for each subject's α value and steady-state maternal serum concentrations (data not shown).

Serum samples were obtained from 11 lactating mothers and their nursing infants. The majority of the pairs of samples were obtained on the same day (N=6), and the remaining samples were collected within 7 days of one another at local pediatric offices or community laboratories. All serum samples from infants were obtained 2–4 hours after morning nursing (8:00–10:00 a.m.). While the majority of the infants' serum samples had undetectable concentrations of sertraline, six infants had detectable concentrations of desmethylsertraline (table 1).

The infants' daily dose was calculated for the six subjects submitting complete breast milk samples for both gradient and time course. In this subgroup, the infants with detectable serum concentrations of both sertraline and desmethylsertraline received higher daily doses. Clearly, the calculated dose in table 1 assumes that the milk concentrations are the same in both breasts and that the infant consumes the entire volume at each feeding. These assumptions and subsequent calculated doses are supported by *detectable* infant serum concentrations observed in the infants receiving greater exposure.

DISCUSSION

The issue of whether to use psychotropic medications during lactation is quite complex. The importance of breast-feeding to the individual mother, the potential

TABLE 1. Concentrations of Sertraline and Desmethylsertraline in 11 Pairs of Mothers and Nursing Infants

Pair	Maternal Medication Dose (mg/day)	Infant's Age (weeks)		Nursing Frequency (times/day)	Infant's Weight (kg)[a]	Infant's Dose (mg/day)[b]		Maternal Serum Concentration (ng/ml)		Infant's Serum Concentration (ng/ml)	
		At Start of Medication	At Serum Sampling			Sertraline	Desmethylsertraline	Sertraline	Desmethylsertraline	Sertraline	Desmethylsertraline
1	25	0	4	7–8	4.9	0.019	0.024	10	25	—[c]	<1.0[d]
2	25	Prenatal	6	6–8	4.7	—[e]	—[e]	11	17	—[c]	9.0
3	50	0	4	6–9	4.5	—[e]	—[e]	21	52	—[c]	1.6
4	50	Prenatal	15	5–7	5.7	0.024	0.023	8	15	—[c]	—[c]
5	50	19	22	5–7	8.6	0.113	0.136	26	45	3.0	10.0
6	100	15	19	5–6[f]	8.0	—[e]	—[e]	19	60	2.7	4.1
7	100	18	25	6–7	7.1	—[e]	—[e]	14	48	<1.0[d]	3.4
8	100	Prenatal	27	4–6[f]	5.5	0.096	0.128	14	29	—[c]	<1.0[d]
9	100	12	30	4–6[f]	8.4	0.075	0.115	38	113	—[c]	—[c]
10	100	137	141	2–3[f]	18.3	—[e]	—[e]	25	66	—[c]	<1.0[d]
11	150	8	18	6–7	6.5	0.124	0.181	92	212	3.0	10.0

[a]At the time of serum sampling.
[b]Calculated as follows:

$$\text{sertraline}=2(\text{total drug/breast at minimum})\sum_{x=t_1}^{t_n}(1.07 + 0.503x - 0.0428x^2 + 0.0001x^3),$$

$$\text{desmethylsertraline}=2(\text{total drug/breast at minimum})\sum_{x=t_1}^{t_n}(1.92 + 0.062x - 0.0075x^2 + 0.00015x^3),$$

where x equals each time point (t) in hours after maternal dose when the infant nursed each day.
[c]Not detectable.
[d]Visual inspection of chromatographs indicated a small peak below the linear portion of the calibration curves.
[e]Not available.
[f]Supplemental feeding more than twice a day.

benefits of nursing to the infant, and the severity of illness must be carefully considered in the risk/benefit analysis of prescribing antidepressants to nursing women. Historically, it has been recommended that nonpharmacological interventions be used before using psychotropic agents or ECT in treating depression in nursing women (1, 2). However, recent changes in health care limit nonpharmacological options such as frequent psychotherapy sessions and inpatient hospitalization without medications. Selective serotonin reuptake inhibitors (SSRIs) are prescribed for a variety of psychiatric disorders, and only limited data are available on their excretion into breast milk and on any potential neurobehavioral effects in nursing infants.

The results of this study indicate that sertraline and its metabolite, like all other antidepressants studied thus far, are present in the breast milk of nursing mothers at concentrations greater than those in maternal serum, although considerable individual variability was evident. The observed breast milk gradient suggests that sertraline and desmethylsertraline are concentrated in the more lipophilic (later) fractions of breast milk. In contrast, a previous report on fluoxetine (20) reported higher fore milk concentrations, although the sample collection procedures in the two studies differed markedly. The effects of a gradient in breast milk may account, in part, for the large variability observed in the time course data for fluoxetine (23). The breast milk concentration of desmethylsertraline was higher than that of sertraline in most cases, and increasing the maternal daily dose increased the concentration of both compounds. A definitive relationship between maternal dose and breast milk concentration would require a larger study group with more than two dose levels to provide clinicians with an accurate estimation of the impact of maternal dose on infant dose.

The raw subject data and mean ratio values shown in figure 1 demonstrate a trend toward increased drug concentrations in the later portions of breast milk. The data and mean ratio values for time course demonstrated the highest breast milk concentrations consistent with the maternal absorptive phase. The time course equations provide a more accurate determination of infant daily dose once actual breast milk concentrations have been determined at a single time point after dose. The equations obtained provide a mechanism for determining an infant's daily dose of sertraline and desmethylsertraline on the basis of a single initial-aliquot breast milk sample obtained 22–24 hours after maternal oral dose. These equations have significant clinical utility. For example, in the case of a lactating woman who is nursing every 3 hours (7–8 feedings per day), the infant's daily dose of sertraline and desmethylsertraline can be reduced by 24.3% and 23.2%, respectively, by discarding a single feeding 7–8 hours after maternal dose (calculated by determining the area under the curve between 7 and 8 hours after maternal dose). The application of the methods in the present study and the development of equations for breast milk excretion are not limited to antidepressants but could be applied to other medications (e.g., antipsychotics, anticonvulsants) in the development of meaningful clinical guidelines to define infant exposure better and to provide a mechanism for limiting infant daily dose.

In the infants with detectable serum concentrations,

sertraline and desmethylsertraline concentrations were higher than we would expect on the basis of the calculated dose of sertraline and desmethylsertraline ingested through nursing, using adult pharmacokinetic data for comparison. This may reflect a prolonged half-life of elimination of the medication by an immature metabolic system. Our results extend the findings of a previous case report (22) and underscore the need to determine drug metabolite concentrations. These concentrations are in marked contrast to a single case report for fluoxetine (20) in which the infant serum concentration was similar to the maternal concentration. Our study confirms the conclusions of Wisner and colleagues (17) that the low concentrations of antidepressants and their metabolites present in infant sera require the use of research-quality assays with well-documented lower limits of sensitivity. The infant serum drug concentrations observed in this study were below the limits of detection of most commercial laboratories (typically, >5.0 ng/ml). Such laboratories usually do not measure active metabolites of antidepressants. The significance of the infant serum concentrations we observed is unknown, but our findings underscore the need to interpret cautiously laboratory results labeled "undetectable," because the limits of the assay may erroneously suggest that infant exposure is minimal. Although no adverse events were reported in the current study (maternal reports), the clinical significance of chronic exposure to an SSRI in neurobehavioral development is unknown. Our group has completed a pilot study of pediatric growth charts and the mothers' reports of developmental milestones achieved, as measured by the Denver Developmental Scale. No significant differences between the infants of lactating depressed women (N=12) and matched non-breast-feeding depressed women (N=12) at 12 months were found (25).

CONCLUSIONS

This study provides a detailed characterization of sertraline excretion into human breast milk; it also represents the most comprehensive study of infant serum concentrations not only of sertraline but of any SSRI. The study provides an initial estimate of risk to infants by defining the extent of drug exposure in infants of nursing mothers being treated with sertraline. Indeed, further scrutiny of the pharmacokinetics of sertraline excretion into breast milk with larger numbers of subjects may support its use as a predictive estimate of infant serum drug concentrations. Pharmacokinetic studies of this type for additional psychotropic medications could provide scientifically derived guidelines for dosage and feeding schedules to limit infant exposure until long-term neurobehavioral follow-up studies are completed.

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